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33

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Annals of Surgery

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Cefotan arithmetic.

+ **more cost-effective than cefoxitin[1,2]**

− **less frequent dosing than cefoxitin[3,4]**

× **several times the half-life of cefoxitin[5,6]**

÷ **single-dose prophylaxis/ twice-daily treatment**

P, 24,806.

Count on

CEFOTAN® IM/IV

(cefotetan disodium)

In intra-abdominal and gynecologic infection due to indicated organisms

References: **1.** Nightingale CH, Smith KS, Quintiliani R, et al: The conversion of cefoxitin usage to cefotetan: An interdisciplinary approach. *Am J Surg* 1988;155(5A):101-102. **2.** Sochalski A, Sullman S, Andriole VT: Cost-effectiveness study of cefotetan versus cefoxitin and cefotetan versus combination antibiotic regimens. *Am J Surg* 1988;155(5A):96-101. **3.** CEFOTAN® (cefotetan disodium) full prescribing information issued March 1986. **4.** *Physicians' Desk Reference*, ed 43. Oradell, NJ, Medical Economics Co, 1989. Mefoxin® (cefoxitin sodium, MSD), pp 1355-1357. **5.** Carver M, Quintiliani R, Nightingale CH: Comparative pharmacokinetic study of cefotetan and cefoxitin in healthy volunteers. *Infect Surg*, April 1986 (suppl), pp 11-14. **6.** Quintiliani R, Nightingale CH, Stevens RC, et al: Comparative pharmacokinetics of cefotetan and cefoxitin in patients undergoing hysterectomies and colorectal operations. *Am J Surg* 1988;155(5A):67-70.

Please see adjacent page for brief summary of prescribing information.

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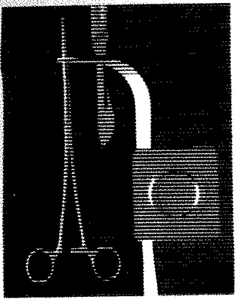

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CEFOTAN® IM/IV (cefotetan disodium)

In intra-abdominal and gynecologic infection due to indicated organisms

For Intravenous or Intramuscular Use
BRIEF SUMMARY

INDICATIONS AND USAGE
TREATMENT: CEFOTAN® (cefotetan disodium) is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:
Urinary tract infections caused by *E coli, Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris, Providencia rettgeri*, and *Morganella morganii*).
Lower respiratory tract infections caused by *Streptococcus pneumoniae* (formerly *D pneumoniae*), *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* species (including *K pneumoniae*), and *E coli*.
Skin and skin structure infections caused by *Staphylococcus aureus* (penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus pyogenes* and *Streptococcus* species (excluding enterococci), and *E coli*.
Gynecologic infections caused by *Staphylococcus aureus** (including penicillinase- and nonpenicillinase-producing strains), *Staphylococcus epidermidis, Streptococcus* species (excluding enterococci), *E coli, Proteus mirabilis, Neisseria gonorrhoeae, Bacteroides* species (excluding *B distasonis, B ovatus, B thetaiotaomicron*), *Fusobacterium* species,* and gram-positive anaerobic cocci (including *Peptococcus* and *Peptostreptococcus* species*).
Intra-abdominal infections caused by *E coli, Klebsiella* species (including *K pneumoniae**), *Streptococcus* species (excluding enterococci), and *Bacteroides* species (excluding *B distasonis, B ovatus, B thetaiotaomicron*).
Bone and joint infections caused by *Staphylococcus aureus*.*
*Efficacy for this organism in this organ system was studied in fewer than ten infections.

Specimens for bacteriological examination should be obtained in order to isolate and identify causative organisms and to determine their susceptibilities to cefotetan. Therapy may be instituted before results of susceptibility studies are known; however, once these results become available, the antibiotic treatment should be adjusted accordingly.

In cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, it is possible to use CEFOTAN concomitantly with an aminoglycoside. Cefotetan combinations with aminoglycosides have been shown to be synergistic in vitro against many Enterobacteriaceae and also some other gram-negative bacteria. The dosage recommended in the labeling of both antibiotics may be given and depends on the severity of the infection and the patient's condition.
NOTE: If CEFOTAN and an aminoglycoside are used concomitantly, renal function should be carefully monitored, especially if higher dosages of the aminoglycoside are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycosidic antibiotics. Although, to date, nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.
PROPHYLAXIS: The preoperative administration of CEFOTAN may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures that are classified as clean contaminated or potentially contaminated (eg, cesarean section, abdominal or vaginal hysterectomy, transurethral surgery, biliary tract surgery, and gastrointestinal surgery).

The prophylactic dose of CEFOTAN should be administered 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, CEFOTAN should be administered intravenously after the clamping of the umbilical cord.

If there are signs and symptoms of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapeutic measures may be initiated.
CONTRAINDICATIONS
CEFOTAN is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.
WARNINGS
Before therapy with CEFOTAN is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cefotetan disodium, cephalosporins, penicillins, or other drugs. This product should be given cautiously to penicillin-sensitive patients. Antibiotics should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CEFOTAN occurs, discontinue the drug. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use.

Treatment with broad-spectrum antibiotics may alter normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis. Cholestyramine and colestipol resins have been shown to bind the toxin in vitro.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte, and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes should also be considered.
PRECAUTIONS
GENERAL: As with other broad-spectrum antibiotics, prolonged use of CEFOTAN may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection does occur during therapy, appropriate measures should be taken.

In common with many other broad-spectrum antibiotics, CEFOTAN may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment or poor nutritional state, the elderly and patients with cancer. Prothrombin times should be monitored in patients at risk and exogenous vitamin K administered as indicated.

CEFOTAN should be used with caution in individuals with a history of gastrointestinal disease, particularly colitis.
INFORMATION FOR PATIENTS: As with some other cephalosporins, a disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia may occur when alcohol (beer, wine, etc.) is ingested within 72 hours after CEFOTAN administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOTAN.
DRUG INTERACTIONS: Although to date nephrotoxicity has not been noted when CEFOTAN was given alone, it is possible that nephrotoxicity may be potentiated if CEFOTAN is used concomitantly with an aminoglycoside.
DRUG/LABORATORY TEST INTERACTIONS: A false positive reaction for glucose in urine may occur with Benedict's or Fehling's solution.

As with other cephalosporins, high concentrations of cefotetan may interfere with measurement of serum and urine creatinine levels by Jaffe reaction and produce false increases in the levels of creatinine reported.
CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Although long-term studies in animals have not been performed to evaluate carcinogenic potential, no mutagenic potential of cefotetan was found in standard laboratory tests.

Cefotetan has adverse effects on the testes of prepubertal rats. Subcutaneous administration of 500 mg/kg/day (approximately 8-16 times the usual adult human dose) on days 6-35 of life (thought to be

CEFOTAN® (cefotetan disodium)

developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approximately 2-4 times the usual human dose) only 1 of 10 treated animals was affected, and the degree of degeneration was mild.

Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-containing antibiotics and impaired fertility has been reported, particularly at high dose levels. No testicular effects were observed in 7-week-old rats treated with up to 1000 mg/kg/day SC for 5 weeks, or in infant dogs (3 weeks old) that received up to 300 mg/kg/day IV for 5 weeks. The relevance of these findings to humans is unknown.
USAGE IN PREGNANCY: Pregnancy Category B: Reproduction studies have been performed in rats and monkeys at doses up to 20 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefotetan. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
USAGE IN NURSING MOTHERS: Cefotetan is excreted in human milk in very low concentrations. Caution should be exercised when cefotetan is administered to a nursing woman.
PEDIATRIC USE: Safety and effectiveness in children have not been established.
ADVERSE REACTIONS
In clinical studies, the following adverse effects were considered related to CEFOTAN therapy.
Gastrointestinal symptoms occurred in 1.5% of patients; the most frequent were diarrhea (1 in 80) and nausea (1 in 700).
Hematologic laboratory abnormalities occurred in 1.4% of patients and included eosinophilia (1 in 200), positive direct Coombs' test (1 in 250), and thrombocytosis (1 in 300).
Hepatic enzyme elevations occurred in 1.2% of patients and included a rise in SGPT (1 in 150), SGOT (1 in 300), alkaline phosphatase (1 in 700), and LDH (1 in 700).
Hypersensitivity reactions were reported in 1.2% of patients and included rash (1 in 150) and itching (1 in 700).
Local effects were reported in less than 1.0% of patients and included phlebitis at the site of injection (1 in 300), and discomfort (1 in 500). During postmarketing experience with CEFOTAN, anaphylactic reactions and transient thrombocytopenia have been reported.
DOSAGE AND ADMINISTRATION
TREATMENT: The usual adult dosage is 1 or 2 grams of CEFOTAN administered intravenously or intramuscularly every 12 hours for 5 to 10 days. Proper dosage and route of administration should be determined by the condition of the patient, severity of the infection, and susceptibility of the causative organism.

GENERAL GUIDELINES FOR DOSAGE OF CEFOTAN

Type of Infection	Daily Dose	Frequency and Route
Urinary Tract	1-4 grams	500 mg every 12 hours IV or IM 1 or 2 g every 24 hours IV or IM 1 or 2 g every 12 hours IV or IM
Other Sites	2-4 grams	1 or 2 g every 12 hours IV or IM
Severe	4 grams	2 g every 12 hours IV
Life-Threatening	6* grams	3 g every 12 hours IV

*Maximum daily dosage should not exceed 6 grams.

PROPHYLAXIS: To prevent postoperative infection in clean contaminated or potentially contaminated surgery in adults, the recommended dosage is 1 or 2 g of CEFOTAN administered once, intravenously, 30 to 60 minutes prior to surgery. In patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped.
IMPAIRED RENAL FUNCTION: When renal function is impaired, a reduced dosage schedule must be employed. The following dosage guidelines may be used.

DOSAGE GUIDELINES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance mL/min	Dose	Frequency
>30	Usual Recommended Dosage*	Every 12 hours
10-30	Usual Recommended Dosage*	Every 24 hours
<10	Usual Recommended Dosage*	Every 48 hours

*Dose determined by the type and severity of infection, and susceptibility of the causative organism.

Alternatively, the dosing interval may remain constant at 12 hour intervals, but the dose reduced to one-half the usual recommended dose for patients with a creatinine clearance of 10-30 mL/min, and one-quarter the usual recommended dose for patients with a creatinine clearance of less than 10 mL/min.

When only serum creatinine levels are available, creatinine clearance may be calculated from the following formula. The serum creatinine level should represent a steady state of renal function.

$$\text{Males:}\quad \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$$

$$\text{Females:}\quad 0.9 \times \text{value for males}$$

Cefotetan is dialyzable and it is recommended that for patients undergoing intermittent hemodialysis, one-quarter of the usual recommended dose be given every 24 hours on days between dialysis and one-half the usual recommended dose on the day of dialysis.
HOW SUPPLIED
CEFOTAN is a dry, white to pale yellow powder supplied in vials containing cefotetan disodium equivalent to 1 g and 2 g cefotetan activity for intravenous and intramuscular administration. The 1 g dose is available in 10 mL and 100 mL vials, and the 2 g dose is available in 20 mL and 100 mL vials. CEFOTAN is also available in a pharmacy bulk package of 10 g in 100 mL vials. The vials should not be stored at temperatures above 22°C and should be protected from light.

1 g in 10 mL vial (NDC 0038-0376-10); 2 g in 20 mL vial (NDC 0038-0377-20); 1 g in 100 mL vial (NDC 0038-0376-11); 2 g in 100 mL vial (NDC 0038-0377-21); 10 g in 100 mL vial (NDC 0038-0375-10).

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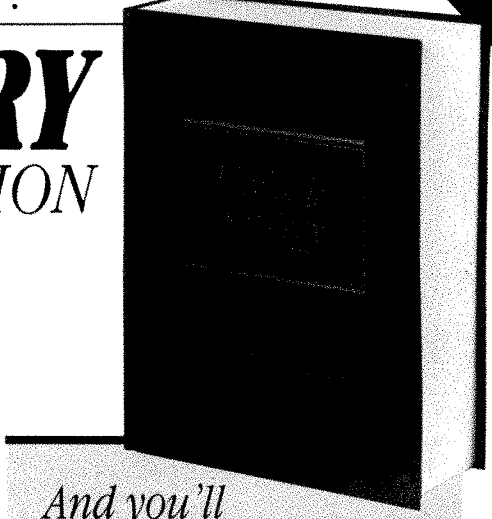

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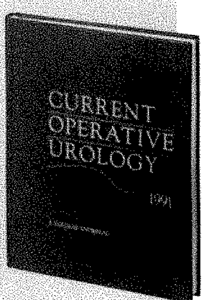

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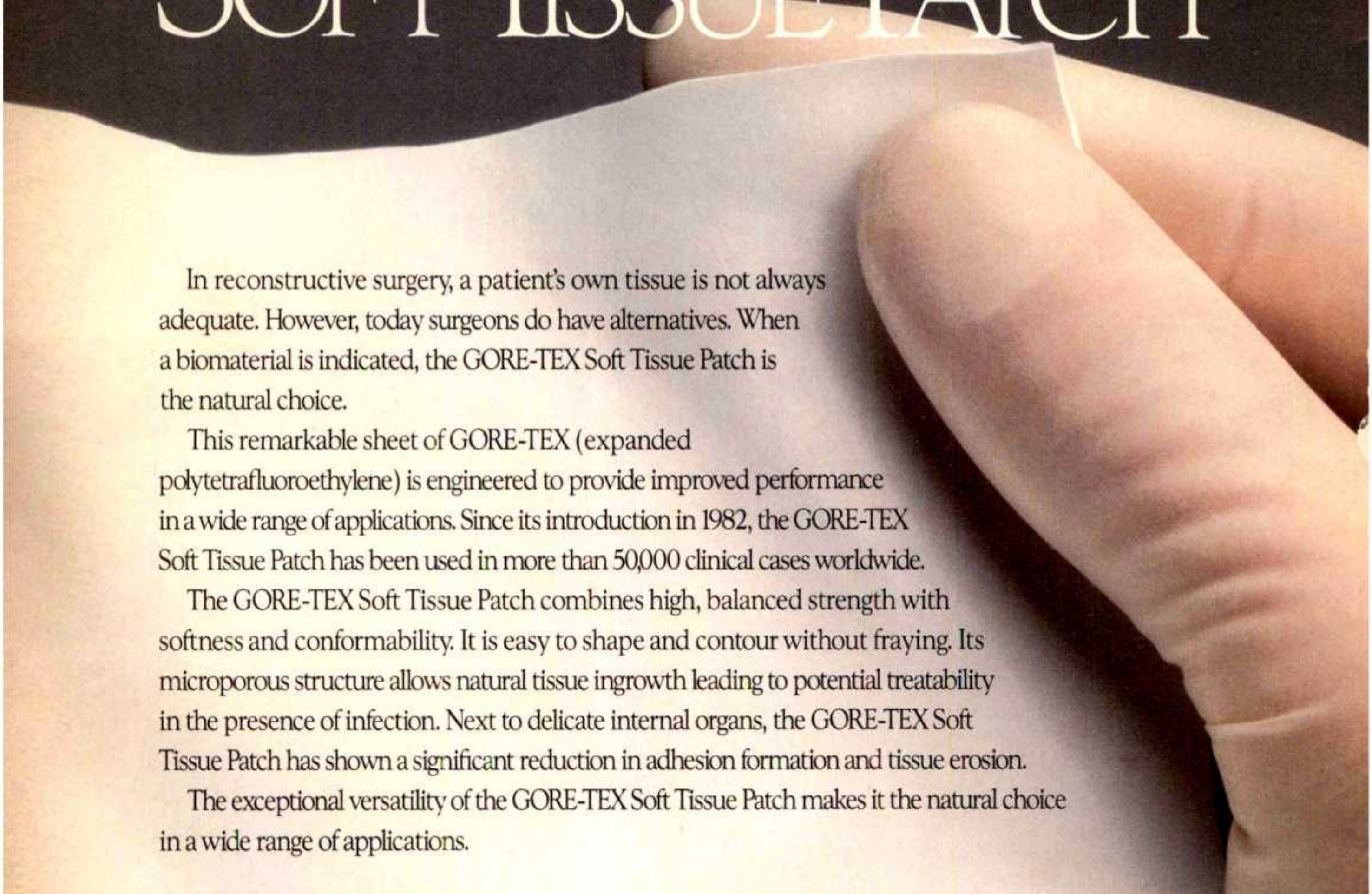

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October 1990

Vol. 212 No. 4

Annals of Surgery

CONTENTS

SCIENTIFIC PAPERS

Impaired Myocardial Function and Oxygen Utilization Due to Protamine Sulfate in an Isolated Rabbit Heart Preparation 387

Protamine sulfate administration, with or without heparin, caused dose- and time-specific adverse effects on cardiac hemodynamics in an isolated rabbit heart preparation. In addition protamine decreased myocardial oxygen extraction and consumption. This is the first time that such effects have been noted in an intact cardiac model.

Thomas W. Wakefield, M.D., Larry E. Bies, B.S., Shirley K. Wrobleski, B.S., Steven F. Bolling, M.D., James C. Stanley, M.D., and Marvin M. Kirsh, M.D.
Ann Arbor, Michigan

Long-term Course of Patients with Persistent Hypercalcitoninemia After Apparent Curative Primary Surgery for Medullary Thyroid Carcinoma 395

Thirty-one patients with persistent hypercalcitoninemia following complete resection of their medullary carcinoma were followed for a mean of 12 years. The 5 and 10-year survival rates were 90% and 86%, respectively.

Jon A. van Heerden, M.B., F.A.C.S., Clive S. Grant, M.D., F.A.C.S., Hossein Gharib, M.D., F.A.C.P., Ian D. Hay, PH.D., F.R.C.P., and Duane M. Ilstrup, M.S.
Rochester, Minnesota

Changing Arteriosclerotic Disease Patterns and Management Strategies in Lower-limb–Threatening Ischemia 402

This 16-year study of 2829 patients with lower-limb–threatening ischemia shows increasing recognition that the condition is caused by multilevel and distal arteriosclerotic lesions. With improved management techniques, almost all patients can be treated effectively and primary and secondary major amputation rates have decreased dramatically.

Frank J. Veith, M.D., Sushil K. Gupta, M.D., Kurt R. Wengerter, M.D., Jamie Goldsmith, R.N., Steven P. Rivers, M.D., Curtis W. Bakal, M.D., Alan M. Dietzek, M.D., Jacob Cynamon, M.D., Seymour Sprayregen, M.D., and Marvin L. Gliedman, M.D.
New York, New York

Selective Evaluation and Management of Coronary Artery Disease in Patients Undergoing Repair of Abdominal Aortic Aneurysms: A 16-year Experience 415

In 500 patients undergoing abdominal aortic aneurysm repair, selective evaluation and management of their cardiac risk was effective, resulting in a mortality rate of 1.6%. Specifically patients with no clinical evidence of coronary disease required no further preoperative cardiac evaluation.

Michael A. Golden, M.D., Anthony D. Whittemore, M.D., Magruder C. Donaldson, M.D., and John A. Mannick, M.D.
Boston, Massachusetts

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October 1990 Vol. 212, No. 4

CONTENTS

Continued

Effects of Recombinant Human Growth Hormone on Donor-site Healing in Severely Burned Children **424**

This study documents the salutory effects of recombinant human growth hormone in a double-blind study of 40 pediatric burn patients. Donor site healing was decreased 2 to 4 days, with a 30% decrease in length of hospital stay and a threefold increase in IGF-1 levels for 18 patients receiving growth hormone supplementation compared to controls.

David N. Herndon, M.D., *Robert E. Barrow,* PH.D., *Kelly R. Kunkel,* M.D., *Lyle Broemeling,* PH.D.,
and Randi L. Rutan, R.N., B.S.N.
Galveston, Texas

Cystic Tumors of the Pancreas: New Clinical, Radiologic, and Pathologic Observations in 67 Patients **432**

The overlapping characteristics of benign and malignant cystic tumors make differential diagnosis difficult and create pitfalls in differentiating the various types from each other and even from pseudocysts. Surgical excision is advisable in most cases.

Andrew L. Warshaw, M.D., *Carolyn C. Compton,* M.D., PH.D., *Kent Lewandrowski,* M.D.,
Gilda Cardenosa, M.D., *and Peter R. Mueller,* M.D.
Boston, Massachusetts

Ileal Pouch–Anal Anastomosis: Reoperation for Pouch-related Complications **446**

The value of reoperative surgery for pouch-related complications was assessed in 114 of 982 ileal pouch–anal anastomosis patients operated for ulcerative colitis or familial adenomatous polyposis. Salvage procedures can be done safely and will restore pouch function in two thirds of patients.

Susan Galandiuk, M.D., *Nigel A. Scott,* M.D., *Roger R. Dozois,* M.D., *Keith A. Kelly,* M.D.,
Duane M. Ilstrup, M.S., *Robert W. Beart, Jr.,* M.D., *Bruce G. Wolff,* M.D., *John H. Pemberton,* M.D.,
Santhat Nivatvongs, M.D., *and Richard M. Devine,* M.D.
Rochester, Minnesota

The Role of Prostanoids in the Production of Acute Acalculous Cholecystitis by Platelet-activating Factor **455**

In the feline model, platelet-activating factor produced acute cholecystitis. The inflammation appeared to be mediated by prostanoids and was inhibited by administration of a cyclooxygenase inhibitor

Donald L. Kaminski, M.D., *Charles H. Andrus,* M.D., *David German,* M.D., *and Yashwant G. Deshpande,* M.S.
St. Louis, Missouri

Multiple Cytokines Are Required to Induce Hepatocyte Nitric Oxide Production and Inhibit Total Protein Synthesis **462**

This study demonstrates a novel metabolic pathway in hepatocytes by which the highly reactive molecule nitric oxide is generated from L-arginine. Exposure to tumor necrosis factor alpha, interferon gamma, interleukin-1 beta, and endotoxin were required to induce hepatocyte nitric oxide biosynthesis, which in turn resulted in an inhibition of hepatocyte total protein synthesis.

Ronald D. Curran, M.D., *Timothy R. Billiar,* M.D., *Dennis J. Stuehr,* PH.D., *Juan B. Ochoa,* M.D.,
Brian G. Harbrecht, M.D., *Susan G. Flint,* B.A., *and Richard L. Simmons,* M.D.
Ithaca, New York

CONTENTS

Continued

Experience with Cardiopulmonary Bypass and Deep Hypothermic Circulatory Arrest in the Management of Retroperitoneal Tumors with Large Vena Caval Thrombi 472

Forty-three patients with large vena caval tumor thrombi from a retroperitoneal malignancy underwent surgical treatment with cardiopulmonary bypass and deep hypothermic circulatory arrest. This approach offers the potential for cure with low morbidity and mortality rates.

Andrew C. Novick, M.D., Mitchell C. Kaye, M.D., Delos M. Cosgrove, M.D., Kenneth Angermeier, M.D., J. Edson Pontes, M.D., James E. Montie, M.D., Stevan B. Streem, M.D., Eric Klein, M.D., Robert Stewart, M.D., and Marlene Goormastic, M.P.H.
Cleveland, Ohio

Urinary Tract Refunctionalization After Long-term Diversion: A 20-year Experience with 177 Patients 478

Undiversion operations were performed using a wide range of techniques in 177 children and young adults previously diverted for various urologic problems. In 32% of cases, the diversion had been present for more than 10 years. There is a means for reconstructing the urinary tract in most of these patients.

W. Hardy Hendren, M.D., F.A.C.S.
Boston, Massachusetts

The Process of Microbial Translocation 496

C. albicans, E. coli, and endotoxin translocated directly through rather than between enterocytes in Thiry-Vella loops in burned guinea pigs and rats. However translocated endotoxin diffused through the submucosa and muscular wall between rather than through myocytes.

J. Wesley Alexander, M.D., SC.D., Steven T. Boyce, PH.D., George F. Babcock, PH.D., Luca Gianotti, M.D., Michael D. Peck, M.D., David L. Dunn, M.D., PH.D., Tonyia Pyles, B.S., Charles P. Childress, M.A.T., and Sara K. Ash, B.S.
Cincinnati, Ohio

Tumor Necrosis Factor-α Mediates Acid Aspiration-induced Systemic Organ Injury 513

After 4 hours, rats locally aspirated with 0.1 NHCl, developed both local and generalized lung leukosequestration and permeability edema. Similar events were noted in the heart and kidney. Treatment with TNF-α antiserum blunted the leukosequestration and edema.

Gideon Goldman, M.D., Richard Welbourn, M.B., F.R.C.S. ED., Lester Kobzik, M.D., C. R. Valeri, M.D., David Shepro, PH.D., and Herbert B. Hechtman, M.D.
Boston, Massachusetts

Upper GI Bleeding in an Urban Hospital: Etiology, Recurrence, and Prognosis 521

In an urban hospital, AGML, gastric ulcer, esophageal varices, and Mallory-Weiss tears are common causes of bleeding with a high recurrence rate, especially with esophageal varices. Significant predictors of mortality include the presence of shock on admission, transfusion requirement of more than five units, and diagnosis of esophageal varices.

Choichi Sugawa, M.D., Christopher P. Steffes, M.D., Ryuji Nakamura, M.D., Joseph J. Sferra, M.D., Chrisann S. Sferra, M.A., Yoshihiko Sugimura, M.D., and David Fromm, M.D.
Detroit, Michigan

Surgical Therapy in Barrett's Esophagus 528

Patients with Barrett's esophagus have a profound loss of esophageal body and sphincter function. The concomitant occurrence of stricture, ulceration, and dysphagia are associated with increased esophageal alkaline exposure probably due to duodenogastric reflux. Both factors are important in planning surgical therapy. Patients with carcinoma were selected for a curative or palliative resection with an acturial 5-year survival of 53% for the former and a median survival with good palliation of 12 months for the latter.

Tom R. DeMeester, M.D., Stephen E. A. Attwood, F.R.C.S.I., Thomas C. Smyrk, M.D., David H. Therkildsen, M.D., and Ronald A. Hinder, M.D.
Omaha, Nebraska

CONTENTS

Continued

Ionized Calcium, Parathormone, and Mortality in Critically Ill Surgical Patients **543**

A prospective study of critically ill surgical patients demonstrated lower ionized calcium and higher parathormone levels in nonsurvivors during the first 4 SICU days. Intracellular migration of calcium is postulated as the etiology of early hypocalcemia. Early hypocalcemia with elevated parathormone is a predictor of mortality risk.

Kenneth W. Burchard, M.D., Donald S. Gann, M.D., Julie Colliton, M.D., and Jameson Forster, M.D.
Hanover, New Hampshire; Baltimore, Maryland; Providence, Rhode Island; and Kansas City, Kansas

Surgical Aspects of Sclerosing Cholangitis: Results in 178 Patients **551**

Of 160 patients with primary and 18 patients with secondary sclerosing cholangitis, 151 had complete follow-up. Median survival time was 9.5 years from diagnosis. Temporary relief of obstructive symptoms was usually obtained by dilatation or anastomosis. Biliary tract distribution of disease and colectomy in inflammatory bowel disease did not influence outcome. Liver transplantation is risky in patients with multiple previous anastomoses and portal shunting.

F. Maureen Martin, M.D., F.R.C.S.(CAN), Ricardo L. Rossi, M.D., F. Warren Nugent, M.D.,
Francis J. Scholz, M.D., Roger L. Jenkins, M.D., W. David Lewis, M.D., Michel Gagner, M.D., F.R.C.S.(CAN),
Eugene Foley, M.D., and John W. Braasch, M.D., PH.D.
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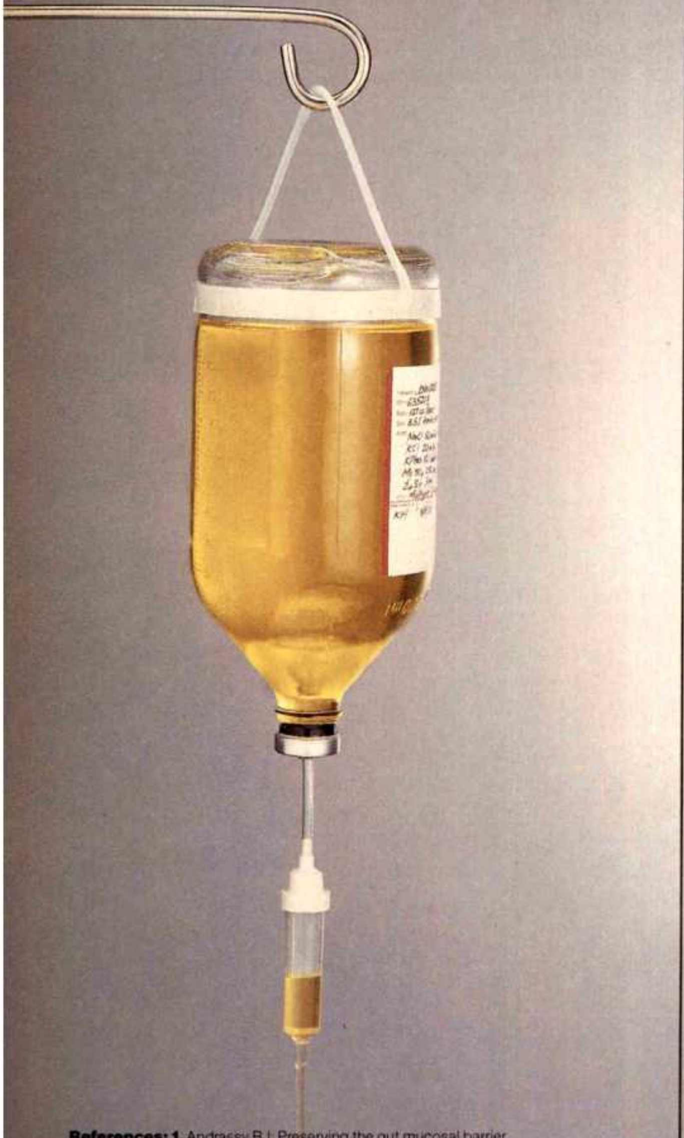

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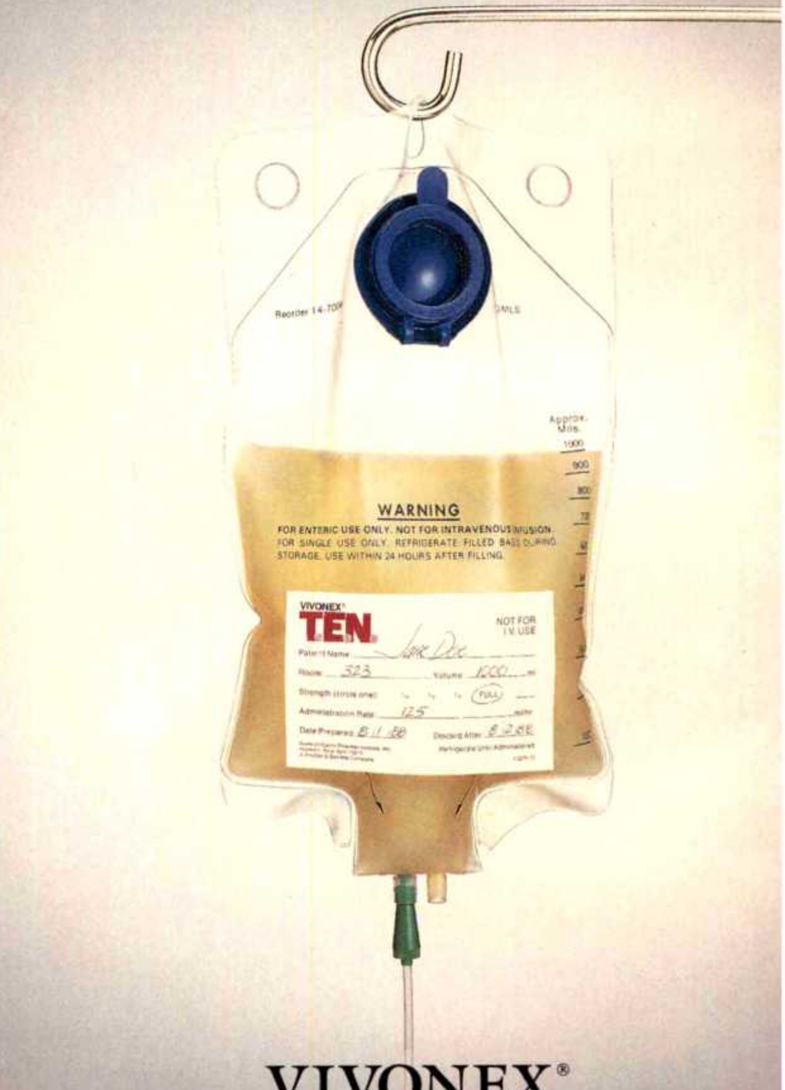
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November 1990
Vol. 212 No. 5

Annals of Surgery

CONTENTS

EDITORIAL

From Monitoring to Predicting Outcome 559
J. G. Reves, M.D. and L. R. Smith, PH.D.
Durham, North Carolina

WHAT'S NEW IN GENERAL SURGERY

The Acutely Affected Abdomen in Paraplegic Spinal Cord Injury Patients 561
Twenty-one paraplegic or quadriplegic patients with 22 acute abdominal episodes are reported. Presenting complaints, physical findings, and laboratory results were of variable utility. However appropriate radiographic studies led to the correct diagnosis in three fourths of the patients.
Leigh A. Neumayer, M.D., David A. Bull, M.D., Jerry D. Mohr, M.D., and Charles W. Putnam, M.D.
Tucson and Phoenix, Arizona

ORIGINAL ARTICLES

Intraoperative Blood Pressure: What Patterns Identify Patients at Risk for Postoperative Complications? 567
Intraoperative hemodynamic patterns do predict postoperative complications. The intraoperative blood pressure should be analyzed in relation to the patient's preoperative blood pressure. Prolonged changes of more than 20 mmHg or 20% in relation to preoperative levels were significantly related to complications.
Mary E. Charlson, M.D., C. Ronald MacKenzie, M.D., Jeffrey P. Gold, M.D., Kathy L. Ales, M.D., Marjorie Topkins, M.D., and G. Tom Shires, M.D.
New York, New York

Results of a Multicenter Trial Comparing Imipenem/Cilastatin to Tobramycin/Clindamycin for Intra-abdominal Infections 581
This study was a multicenter comparative trial of two antibiotic regimens for intra-abdominal infections in 162 patients with outcome analysis based on severity of illness scoring. The results showed significant improvement in outcome with imipenem/cilastatin.
Joseph S. Solomkin, M.D., E. Patchen Dellinger, M.D., Nicolas V. Christou, M.D., PH.D., and Ronald Busuttil, M.D., PH.D.
Cincinnati, Ohio; Seattle, Washington; Montreal, Quebec, Canada; and Los Angeles, California

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CONTENTS

Continued

Positive Results of Combined Therapy of Surgery and Intraperitoneal Hyperthermic Perfusion for Far-advanced Gastric Cancer **592**

Intraperitoneal hyperthermic perfusion (IPHP) using mitomycin C combined with surgery was performed on 30 patients with far-advanced gastric cancer. The 30 patients given IPHP lived longer at p = 0.001 than 29 patients without IPHP, with a 1-year survival rate of 80.4% in the former *versus* 34.2% in the latter.

Shigeru Fujimoto, M.D., *Ram Dhoj Shrestha,* M.D., *Masashi Kokubun,* M.D., *Kokuriki Kobayashi,* M.D.,
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Chiba, Japan

Parietal Cell Vagotomy and Dilatation for Peptic Duodenal Stricture **597**

Parietal cell vagotomy and dilatation for peptic duodenal stricture revealed an ulcer recurrence rate of 21.8% after 6 to 10 years follow-up.

Ali Ş. Menteş, M.D.
Izmir, Turkey

Intrarectal Ultrasonography in Rectal Cancer Staging and in the Evaluation of Pelvic Disease: Clinical Uses of Intrarectal Ultrasound **602**

In a prospective study, staging of rectal cancer patients was significantly more accurate using intrarectal ultrasonography than digital exam. Ultrasound exam also identified positive lymph nodes in many patients and demonstrated promise in a separate patient group in the evaluation of perirectal-pelvic pathology.

Jeffrey W. Milsom, M.D. *and Hans Graffner,* M.D., PH.D.
Grand Rapids and East Lansing, Michigan; and Helsingborg, Sweden

Localization and Peptide Content of Endocrine Pancreatic Tumors **607**

The role of selective pancreatic vein sampling and the peptide pattern in 31 endocrine pancreatic tumors was studied. The vein sampling procedure was positive in all cases performed and most tumors were multihormonal.

Hans Mårtensson, M.D., PH.D., *Gerhard Böttcher,* M.D., *Frank Sundler,* M.D., PH.D.,
and Anders Nobin, M.D., PH.D.
Lund, Sweden

Localization and Surgical Treatment of Occult Insulinomas **615**

Twelve patients with biochemical evidence of insulinoma and negative radiographic imaging studies underwent portal venous sampling (PVS) for insulin concentration and surgical exploration with operative ultrasound (IOUS). Eleven patients had insulinomas removed and were cured, despite the fact that operative palpation only identified five tumors. IOUS identified 10 occult insulinomas and PVS localized the other tumor.

Jeffrey A. Norton, M.D., *Thomas H. Shawker,* M.D., *John L. Doppman,* M.D., *Donald L. Miller,* M.D.,
Douglas L. Fraker, M.D., *Douglas T. Cromack,* M.D., *Phillip Gorden,* M.D., *and Robert T. Jensen,* M.D.
Bethesda, Maryland

Surgical Management of Pheochromocytoma with the Use of Metyrosine **621**

This report reviews preoperative and operative management of 25 patients with pheochromocytoma, in particular evaluating the preoperative use of phenoxybenzamine and metyrosine. The combined regimen of phenoxybenzamine and metyrosine provides an excellent means of blood pressure control and provides some potential advantages over use of phenoxybenzamine alone.

Roger R. Perry, M.D., *Harry R. Keiser,* M.D., *Jeffrey A. Norton,* M.D., *Russel T. Wall,* M.D.,
Cary N. Robertson, M.D., *William Travis,* M.D., *Harvey I. Pass,* M.D., *McClellan M. Walther,* M.D.,
and W. Marston Linehan, M.D.
Bethesda, Maryland

November 1990 Vol. 212, No. 5

CONTENTS

Continued

Does Carotid Restenosis Predict an Increased Risk of Late Symptoms, Stroke, or Death? ... **629**

Carotid stenosis after endarterectomy was not associated with an increased likelihood of late stroke or shortened life span when compared with the outlook of patients who did not have restenosis.

Eugene F. Bernstein, M.D., PH.D., *Schlomo Torem,* M.D., *and Ralph B. Dilley,* M.D.
La Jolla, California

Alanyl-glutamine Counteracts the Depletion of Free Glutamine and the Postoperative Decline in Protein Synthesis in Skeletal Muscle ... **637**

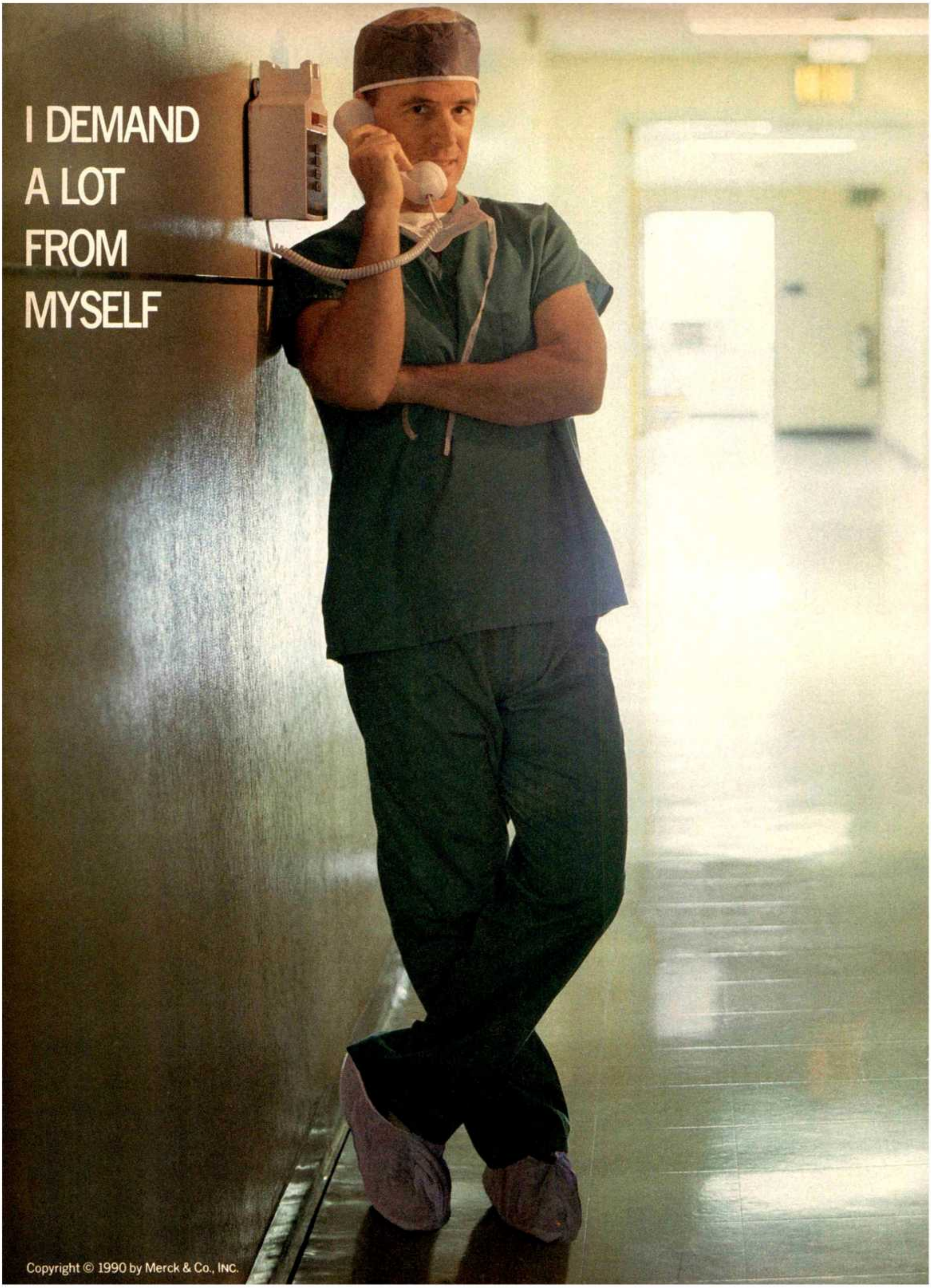
Cholecystectomy is used as a standardized human trauma model to evaluate the effect of a glutamine-containing dipeptide on skeletal muscle protein metabolism during the 3 days immediately following surgery.

Folke Hammarqvist, M.D., PH.D., *Jan Wernerman,* M.D., PH.D., *Alexandra von der Decken,* PH.D.,
and Erik Vinnars, M.D., PH.D.
Stockholm, Sweden

BOOK REVIEWS ... **645**

LETTERS TO THE EDITOR ... **648**

Please see the March 1990 issue for the complete Notice to Contributors and Subscribers.



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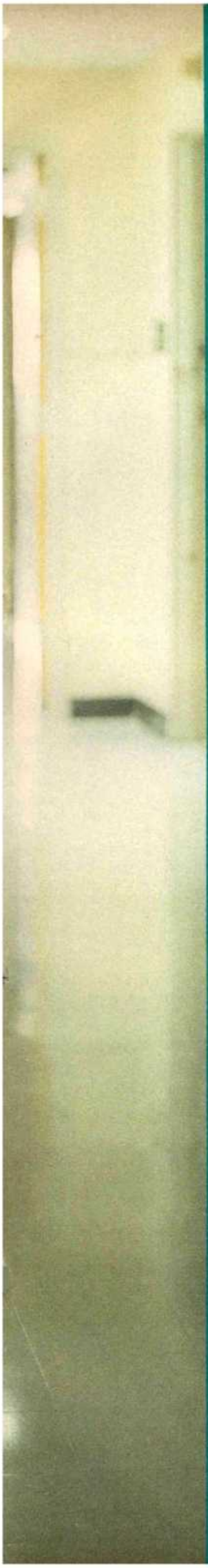

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EPTICEMIA caused by *Strep. pneumoniae*, *Staph. aureus* (penicillinase and non-penicillinase producing), *coli*, *Klebsiella* species, and *Bacteroides* species including the *B. fragilis* group*
ONE AND JOINT INFECTIONS caused by *Staph. aureus* (penicillinase and non-penicillinase producing).
KIN AND SKIN STRUCTURE INFECTIONS caused by *Staph. aureus* (penicillinase and non-penicillinase roducing), *Staph. epidermidis*, streptococci (excluding enterococci, e.g., *Strep. faecalis*), *E. coli*, *P. mirabilis*, *lebsiella* species, *Bacteroides* species including the *B. fragilis group,** *Clostridium* species, *Peptococcus* pecies, and *Peptostreptococcus* species.
lthough appropriate culture and susceptibility studies should be performed, therapy may be started while waiting these results. Cefoxitin is not active *in vitro* against most strains of *Pseudomonas aeruginosa* and nterococci (e.g., *Strep. faecalis*) and many strains of *Enterobacter cloacae*. Methicillin-resistant staphylo-occi are almost uniformly resistant to cefoxitin.
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ontraindications: Previous hypersensitivity to cefoxitin and the cephalosporin group of antibiotics.
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seudomembranous colitis, from mild to life-threatening in severity, has been reported with irtually all antibiotics (including cephalosporins); therefore, it is important to consider its iagnosis when diarrhea develops in association with antibiotic use. Broad-spectrum antibiotics lter normal flora of colon and may permit overgrowth of clostridia; a toxin produced by *Clostridium difficile* a primary cause of antibiotic-associated colitis. Mild cases may respond to drug discontinuance alone; in ore severe cases, management may include sigmoidoscopy, appropriate bacteriological studies, fluid, lectrolyte and protein supplementation, and use of a drug such as oral vancomycin; isolation of the patient may be advisable. Other causes of colitis should also be considered.
Precautions: *General*—Total daily dose should be reduced in patients with reduced urinary output due to renal insufficiency because high and prolonged serum antibiotic concentrations can occur from usual doses. Prescribe with caution in patients with a history of gastrointestinal disease, particularly colitis. Prolonged use may result in overgrowth of nonsusceptible organisms; repeated evaluation of the patient's condition is essential. If superinfection occurs, take appropriate measures.
Drug Interactions—Increased nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside antibiotics.
Drug/Laboratory Test Interactions—High concentrations (>100 mcg/mL) may interfere with measurement of serum and urine creatinine levels by the Jaffé reaction and produce false increases of modest degree in creatinine levels reported; serum samples should not be analyzed for creatinine if withdrawn within 2 hours of cefoxitin administration. High concentrations may interfere with measurement of urinary 17-hydroxy-corticosteroids by the Porter-Silber reaction and produce false increases of modest degree in levels reported. A false-positive reaction for glucose in urine has been observed with CLINITEST** reagent tablets.
Carcinogenesis, Mutagenesis, Fertility Impairment—No long-term animal study has been performed on carcinogenic or mutagenic potential. Rat studies at approximately three times maximum recommended human dosage revealed no effects on fertility or mating ability.
Pregnancy Category B—Reproduction studies in rats and mice did not reveal teratogenic or fetal toxic effects, although fetal weights were slightly decreased. In rabbits, cefoxitin was associated with a high incidence of abortion and maternal death, neither considered teratogenic. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers—Excreted in human milk; Exercise caution.
Pediatric Use—Safety and efficacy in infants from birth to three months have not yet been established. In children three months and older, higher doses have been associated with increased incidence of eosinophilia and elevated SGOT.
Adverse Reactions: The most common adverse reactions have been local reactions following intravenous or intramuscular injection. Other adverse reactions have been encountered infrequently. *Local Reactions*—Thrombophlebitis with intravenous administration; pain, induration, and tenderness after intramuscular injections. *Allergic Reactions*—Rash (including exfoliative dermatitis), pruritus, eosinophilia, fever, and other allergic reactions including anaphylaxis. *Cardiovascular*—Hypotension. *Gastrointestinal*—Diarrhea, including documented pseudomembranous colitis during or after treatment, and, rarely, nausea and vomiting. *Blood*—Eosinophilia, leukopenia including granulocytopenia, neutropenia, anemia, including hemolytic anemia, thrombocytopenia, and bone marrow depression. A positive direct Coombs test may develop in some individuals, especially those with azotemia. *Liver Function*—Transient elevations in SGOT, SGPT, serum LDH, and serum alkaline phosphatase; jaundice. *Renal Function*—Elevations in serum creatinine and/or blood urea nitrogen levels and, rarely, acute renal failure.
Note: In group A beta-hemolytic streptococcal infections, therapy should be maintained for at least 10 days to guard against the risk of rheumatic fever or glomerulonephritis. In staphylococcal and other infections involving a collection of pus, surgical drainage should be carried out where indicated. Intramuscular injections should be well within the body of a relatively large muscle such as the upper outer quadrant of the buttock (i.e., gluteus maximus); aspiration is necessary to avoid inadvertent injection into a blood vessel. The total daily dosage in infants and children should not exceed 12 grams.
How Supplied: Sterile cefoxitin sodium in vials, infusion bottles, and ADD-Vantage®† vials containing 1 gram or 2 grams cefoxitin equivalent and in 10-gram bulk bottles.

B. fragilis, B. distasonis, B. ovatus, B. thetaiotaomicron, B. vulgatus

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December 1990

Vol. 212 No. 6

Annals of Surgery

CONTENTS

EDITORIAL

Sepsis and Tumor Necrosis Factor—Bedfellows that Cannot Be Ignored 653

Hamish R. Michie, F.R.C.S., and Douglas W. Wilmore, M.D., F.A.C.S.
Oxford, United Kingdom and Boston, Massachusetts

WHAT'S NEW IN GENERAL SURGERY

Hepatic Abscess: Changes in Etiology, Diagnosis, and Management 655

A computerized analysis of multiple clinical parameters in 73 patients with pyogenic hepatic abscess emphasizes that the primary determinant of outcome was the underlying disease rather than solitary *versus* multiple abscesses. Some suggestions are made with respect to current clinical management of this potentially grave disease.

Gene D. Branum, M.D., George S. Tyson, M.D., Mary A. Branum, R.N., and William C. Meyers, M.D.
Durham, North Carolina

ORIGINAL ARTICLES

The Effects of Tumor Necrosis Factor on Intestinal Structure and Metabolism 663

Tumor necrosis factor may limit substrate available to the intestinal tract, which could jeopardize rapid cell proliferation and mucosal repair.

J. J. B. van Lanschot, M.D., K. Mealy, M.D., and D. W. Wilmore, M.D.
Boston, Massachusetts

The Effect of Ambulation on Recovery from Postoperative Ileus 671

The gastric, jejunal, and colonic myoelectric activity patterns of 10 patients after an early postoperative ambulation regimen were not significantly different from a control group of 24 patients. The data suggest that ambulation as a means to resolve postoperative ileus may be more perceived than real.

John H. T. Waldhausen, M.D., and Bruce D. Schirmer, M.D.
Charlottesville, Virginia

Efficacy of Octreotide Acetate in Treatment of Severe Postgastrectomy Dumping Syndrome 678

Octreotide acetate was shown to be highly effective in ablating acute and chronic symptoms of severe postgastrectomy dumping syndrome.

Richard J. Geer, M.D., William O. Richards, M.D., Thomas M. O'Dorisio, M.D., Eugene O. Woltering, M.D., Shauna Williams, M.D., Donna Rice, R.N., and Naji N. Abumrad, M.D.
Nashville, Tennessee; Columbus, Ohio; and Portland, Oregon

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CONTENTS

Continued

**Reperfusion Inhibits Elevated Splanchnic Prostanoid Production Afte
Hemorrhagic Shock** . . . .

Acute hemorrhagic shock to 30 mmHg for 30 minutes induced a splanchnic compens
increased release of prostacyclin (potent vasodilator) *in vitro* in the rat. Reperfusion o
hemorrhagic shock abolished splanchnic prostacyclin release.

Stuart I. Myers, M.D., F.A.C.S., Betty J. Taylor, B.S., and Maria Stanislawska
Houston, Texas

**Evidence for Tumor Necrosis Factor-induced Pulmonary Microvascul
Intestinal Ischemia–Reperfusion Injury** . . . .

Acute lung injury occurs after experimental intestinal ischemia–reperfusion. Data esta
relationship between this lung injury and plasma tumor necrosis factor (TNF) levels a
addition, anti-TNF antibody is shown to attenuate the increase in pulmonary microva

*Michael G. Caty, M.D., Karen S. Guice, M.D., Keith T. Oldham, M.D., Daniel G. Remi
and Steven I. Kunkel, M.D.*
Ann Arbor, Michigan

Blunt Traumatic Cardiac Rupture: A 5-Year Experience . . . .

Twelve of thirty-two patients with cardiac rupture after blunt trauma had vital signs a
survived after diagnosis by thoracotomy or subxiphoid window and primary repair wi
bypass. Rapid prehospital transportation, a high index of suspicion, and prompt surgic
contribute to higher survival rates.

*Collin E. M. Brathwaite, M.D., Aurelio Rodriguez, M.D., S. Z. Turney, M.D., C. M. Du
and RA. Cowley, M.D.*
Baltimore, Maryland

**Treatment of Patients with Aortic Dissection Presenting with Periphe
Complications** . . . .

The incidence of peripheral vascular complications and clinical outcome was assessed
acute or chronic aortic dissections. Eighty-five patients (31%) sustained one or more p
complications (including stroke, paraplegia, peripheral pulse, loss, or impaired renal o
Multivariate analysis demonstrated that only compromised renal perfusion was linked
operative mortality risk. Following surgical repair of the thoracic aorta, local periphera
were unnecessary in 92% of patients who presented with absence of a peripheral pulse.

*James I. Fann, M.D., George E. Sarris, M.D., R. Scott Mitchell, M.D., Norman E. Shum
Edward B. Stinson, M.D., Philip E. Oyer, M.D., and D. Craig Miller, M.D.*
Stanford, California

The Risk of Large Bowel Cancer After Partial Gastrectomy for Benig

Following partial gastrectomy for ulcer disease, the risk of developing colorectal cance
about 25% during the first 19 years of a follow-up and close to the expected thereafter.
with a longer duration of follow-up might be a consequence of the surgical procedure i

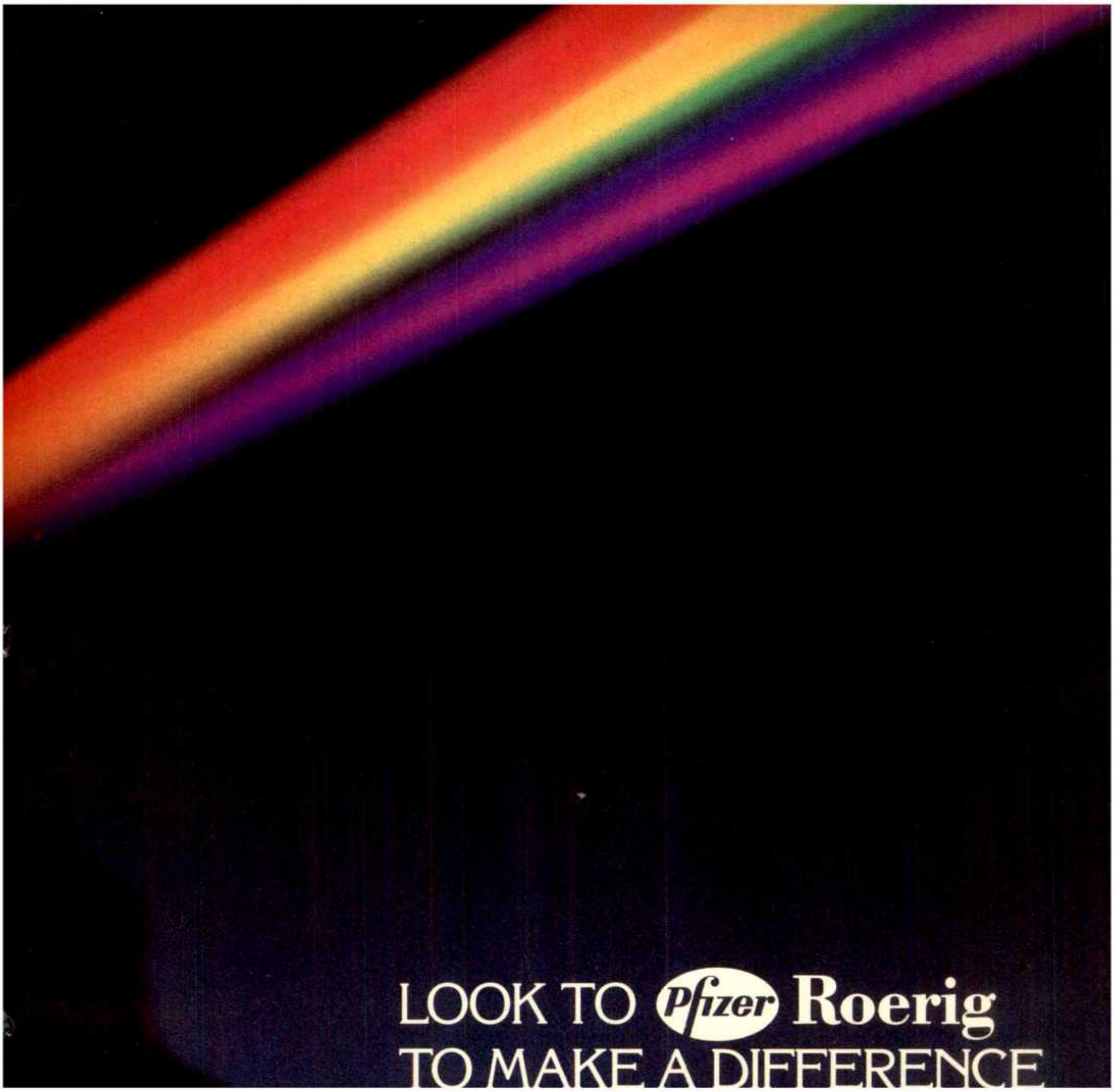
*Göran Lundegårdh, M.D., Hans-Olov Adami, M.D., PH.D., Charles Helmick, M.D., and
Matthew Zack, M.D., M.P.H.*
Boden and Uppsala, Sweden and Atlanta, Georgia

The Role of Inhalation Injury in Burn Trauma: A Canadian Experienc

A 10-year review of 1705 thermally injured Canadian patients was conducted. Inhalati
increase morbidity and mortality rates significantly independent of age and total body-
in a highly variable nonquantifiable manner.

*Edward E. Tredget, M.SC., M.D., Heather A. Shankowsky, R.N., Terry V. Taerum, PH.D.
Gerald L. Moysa, M.D., and John D. M. Alton, M.D.*
Edmonton, Alberta, Canada

LAST YEAR 70,000 PEOPLE DIED
FROM ENDOTOXIC SHOCK[1]


LOOK TO Pfizer Roerig
TO MAKE A DIFFERENCE

December 1990 Vol. 212, No. 6

CONTENTS

Continued

Involvement of Thromboxane and Neutrophils in Multiple-system Organ Edema with Interleukin-2 .... **728**
A 1-hour but not a 1-minute infusion of interleukin-2 will induce thromboxane synthesis, lung leukosequestration, and edema of the lungs, heart, liver, and kidney. These findings may assist in developing therapeutic strategies.
Richard Welbourn, M.B., F.R.C.S.ED., Gideon Goldman, M.D., Lester Kobzik, M.D., C. R. Valeri, M.D., David Shepro, PH.D., and Herbert B. Hechtman, M.D.
Boston, Massachusetts

Subject Index to Volume 212 .... **735**

Author Index to Volume 212 .... **739**

Please see the March 1990 issue for the complete Notice to Contributors and Subscribers.

SCIENTIFIC PAPERS

Impaired Myocardial Function and Oxygen Utilization Due to Protamine Sulfate in an Isolated Rabbit Heart Preparation

THOMAS W. WAKEFIELD, M.D., LARRY E. BIES, B.S., SHIRLEY K. WROBLESKI, B.S., STEVEN F. BOLLING, M.D., JAMES C. STANLEY, M.D., and MARVIN M. KIRSH, M.D.

The myocardial effects of protamine, with and without heparin, were documented in this investigation. Isolated rabbit hearts (n = 30) were retrograde perfused with Krebs–Ringers bicarbonate solution aerated with 95% O_2/5% CO_2 through the aortic root (37 C, 80 mmHg). Developed left ventricular blood pressure, heart rate, coronary artery flow, contractility as reflected by peak +dp/dt, oxygen extraction (a–vO_2), and oxygen consumption ($\dot{V}O_2$) were measured at baseline and continuously throughout the experiment. Protamine (25 µg, 50 µg, and 250 µg per mL of perfusate) was circulated in the Krebs–Ringers buffer to hearts perfused without heparin (groups I, II, and III) or hearts perfused with heparin added to the buffer solution, 0.1 IU/1.0 µg protamine (groups IV, V, and VI). Blood pressure 4 minutes after protamine was less in groups III (−23 mmHg) and VI (−28 mmHg) than in groups I (−6 mmHg), II (−18 mmHg), IV (−1 mmHg), and V (−7 mmHg). Heart rate changes (beats/minute) at 4 minutes revealed similar dose-dependent reductions (III and VI: −51, −55; II and V: −36, −36; and I and IV: −20, −16, respectively). Coronary artery flow at 4 minutes was slightly increased in groups III (9 mL/minute) and VI (15 mL/minute), but was relatively unchanged in the other groups. Decreases in contractility were apparent in all groups 4 minutes after protamine was started: group I, −14%; II, −16%; III, −30%; IV, −7%; V, −15%; and VI, −34%. Similarly declines in oxygen extraction and consumption were noted in all groups at the same time period and were greater in groups III (−53%†, −44%†) and VI (−55%†, −49%†) than in groups I (−25%†, −26%†), II (−15%*, −12%), IV (−48%†, −49%†) and V (−15%, −18%*), with $p \le 0.05$* or $p \le 0.01$† compared to baseline. Three of ten hearts exposed to high-dose protamine stopped beating after 5 minutes. This investigation establishes, for the first time, that protamine has dose- and time-specific adverse effects on cardiac contractility. In addition protamine decreases myocardial a–vO_2 and $\dot{V}O_2$. These changes may contribute to certain adverse events accompanying the clinical administration of protamine.

From the Sections of Vascular and Thoracic Surgery, the Department of Surgery, University of Michigan Medical Center, Ann Arbor, Michigan

PROTAMINE SULFATE ADMINISTRATION is associated with a number of adverse side effects, including systemic hypotension, bradycardia, pulmonary artery hypertension or hypotension, thrombocytopenia, and leukopenia.[1-11] In addition significant declines in oxygen consumption have been noted to accompany these events in canine experiments[12] and humans undergoing aortic aneurysmectomy (unpublished observations). Although it was thought earlier that protamine did not cause specific myocardial depression,[13-15] several recent studies have demonstrated that high concentrations of protamine directly depress isolated myocardial muscle-strip mechanics.[16-19] The present investigation documents the cardiac and metabolic effects of protamine, with and without heparin, in a modified Langendorff whole-rabbit heart model.

Methods

Hearts from 30 adult New Zealand white rabbits (average weight, 3 kg) were studied. Each animal was anesthetized with pentobarbital sodium (25 mg/mL) and the hearts removed through median sternotomy was immediately placed in cold 4 C modified Krebs–Ringers bicarbonate solution. The aorta was cannulated and connected to a primary perfusion column containing Krebs–Ringers bicarbonate solution aerated with 95% O_2/5% CO_2, free of formed blood elements. The heart was perfused in a retrograde manner through the aortic root at 37 C and a pressure of 80 mmHg (Fig. 1). The perfusate contained 118 mmol/L (millimolar) NaCl, 4 mmol/L KCl, 22.32 mmol/L $NaHCO_3$, 11.1 mmol/L dextrose, 0.66 mmol/L KH_2PO_4, 1.23 mmol/L $MgCl_2$, and 2.38 mmol/L $CaCl_2$.

Presented at the 110th Annual Meeting of the American Surgical Association, Washington, D.C., April 5–7, 1990.

Address reprint requests to Thomas W. Wakefield, M.D., University Hospital, 2210 THCC, 1500 East Medical Center Dr., Ann Arbor, Michigan 48109-0329.

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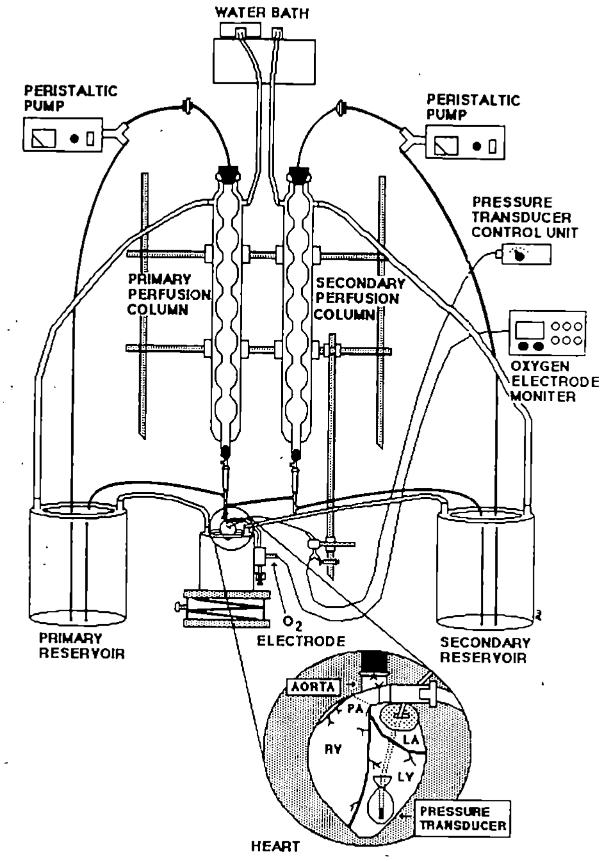

FIG. 1. Schematic drawing of the isolated heart perfusion apparatus. The perfusion solution bubbled with 95% O_2/5% CO_2, with or without heparin, is pumped from the primary reservoir by a peristaltic pump (Monostat, New York, NY) to a height that allows for gravity-driven perfusion through the primary perfusion column at 80 mmHg to the heart. After a 30-minute period of stabilization, protamine solution in the secondary reservoir, again bubbled with 95% O_2/5% CO_2, is then perfused through the secondary perfusion column into the heart in the same manner with another peristaltic pump and gravity. Hemodynamics are recorded on-line onto a computer with a pressure transducer placed into the left ventricle and connected to a control unit (Millar Instruments, Inc., Houston, TX). An oxygen (O_2) electrode (Diamond General Corp, Ann Arbor, MI) is used to continuously measure the level of oxygen in the pulmonary artery effluent and recorded on a monitor. Collected pulmonary artery effluent is measured on an every-other-minute basis to determine coronary artery flow, and the entire circuit is maintained at 37 C by a circulating heated water bath (Haake, FGR).

Developed left ventricular blood pressure (LVBP), representing the difference between peak-systolic and end-diastolic blood pressure; heart rate (HR); and coronary artery flow (CaQ) were measured at baseline after a 30-minute stabilization period and continuously throughout the experiment. Oxygen extraction (a–vO_2), calculated as the arteriovenous difference in oxygen content, was recorded as a percentage. Oxygen consumption ($\dot{V}O_2$), calculated by the arteriovenous difference in oxygen content multiplied by the coronary artery flow, was recorded in milliliters per minute. Contractility was assessed by calculation of peak +dp/dt. Protamine sulfate (Eli Lilly, Indianapolis, IN) was circulated from the secondary column in three different perfusate concentrations (25, 50, and 250 μg/mL) to hearts that were perfused with buffer alone from the primary column (groups I, II, and III) or to hearts that were perfused with heparin sodium, 0.1 IU/1.0 μg protamine (Upjohn Co., Kalamazoo, MI) added to the buffer in the primary column (groups IV, V, and VI). Each study group consisted of five separate heart preparations. Individual experiments lasted for up to 15 minutes or until the heart was no longer contractile. This experimental preparation has been used extensively for many cardiac investigations and the hearts are stable with little or no declines in hemodynamic parameters attributed to the preparation itself.[20,21] In fact data from our laboratory have revealed no change in hemodynamic parameters during a 3-hour time period using the present preparation. Maximum $\dot{V}O_2$ declines of 4% per hour were noted with a similar rabbit heart preparation using a normoxic Tyrode solution perfusate, while a–vO_2 actually increased during the same time period.[22]

Animal care complied with the *Principles of Laboratory Animal Care* and the *Guide for the Care and Use of Laboratory Animals* (NIH No. 80-23, Revised 1985). Results were subjected to statistical analysis using analysis of variance (ANOVA), unpaired t test, and paired t test for parametric data, and Kruskal-Wallis, Mann-Whitney, and Wilcoxon signed rank tests for nonparametric data.

Results

Three of ten hearts subjected to high concentrations of protamine sulfate (250 μg/mL), including both heparinized and nonheparinized hearts, stopped beating after 5 minutes. It was elected to compare results 4 minutes after protamine was begun so these hearts were not excluded from analysis. Declines in LVBP were greater after exposure to high-dose protamine, groups III (−23 mmHg) and VI (−28 mmHg) than with lesser exposure, groups I (−6 mmHg), II (−18 mmHg), IV (−1 mmHg) and V (−7 mmHg). However ANOVA revealed no statistically significant differences between these groups ($p = 0.146$, ns). Maximum declines in LVBP were seen 15 minutes after the protamine perfusion was instituted in groups III (−61 mmHg, $p \leq 0.05$ compared to baseline) and VI (−55 mmHg, $p \leq 0.05$ compared to baseline). Dose-dependent reductions in LVBP were clearly evident in groups I, II, and III without heparin exposure, as well as in groups IV, V, and VI with heparin exposure (Fig. 2).

Heart rate changes 4 minutes after beginning the protamine infusion exhibited similar dose-dependent reductions (groups III and VI −51, −55 beats/minute, respectively; groups II and V −36, −36 beats/minutes, respectively; $p \leq 0.01$ compared to baseline for both; groups I and IV −20, −16 beats/minute, respectively; $p \leq 0.05$ compared to baseline for both; Fig. 3). Maximum changes in HR compared to baseline were group I (−31, $p \leq 0.05$),

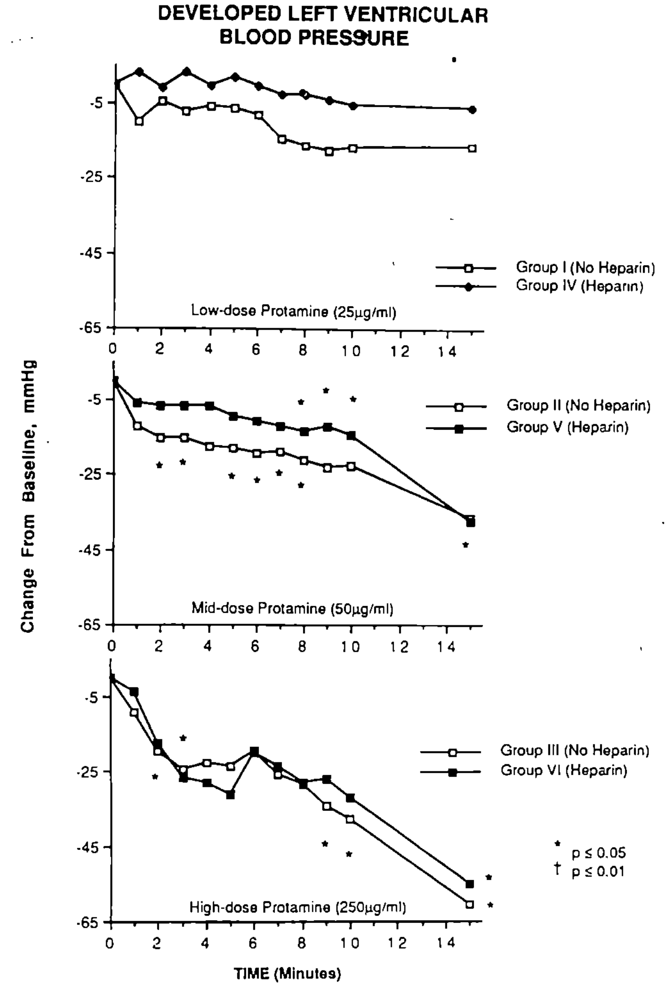

FIG. 2. Change in developed left ventricular blood pressure, groups I, II, and III with no heparin and groups IV, V, and VI with heparin, 0.1 IU/1.0 μg protamine.

group II (−89, $p \leq 0.01$), group III (−100, $p \leq 0.01$), group IV (−25), group V (−106, $p \leq 0.01$), and group VI (−95, $p \leq 0.05$). No statistically significant difference between the groups was evident 4 minutes after beginning protamine (ANOVA, $p = 0.339$).

Coronary artery flow 4 minutes after protamine exposure was begun was not statistically different among the groups (ANOVA, $p = 0.65$). A slight increase was evident in groups III (9 mL/minute) and VI (15 mL/minute), but little change was observed in the other groups (I − 1 mL/minute, II 1 mL/minute, IV 3 mL/minute, and V − 1 mL/minute, respectively). Coronary artery flow in group III increased significantly 6, 8, and 10 minutes after beginning protamine compared to baseline, while in all other groups CaQ was affected very little by protamine exposure (Fig. 4).

Contractility, as assessed by changes in peak +dp/dt, varied among the test groups (Kruskal-Wallis, $p = 0.05$) although there appeared to be no difference in the three protamine dosages among hearts exposed and unexposed to heparin. Declines in peak +dp/dt compared to baseline, 4 minutes after initiating the protamine perfusion, were greater in groups III (−30%, $p \leq 0.05$) and VI (−34%, $p \leq 0.05$) than in groups I (−14%, $p \leq 0.05$), II (−16%), IV (−7%, $p \leq 0.05$), and V (−15%, $p \leq 0.01$). Maximum declines in peak +dp/dt compared to baseline were group I (−20%, $p \leq 0.05$), group II (−25%, $p \leq 0.05$), group III (−66%, $p \leq 0.05$), group IV (−10%, $p \leq 0.05$), group V (−47%, $p \leq 0.05$), and group VI (−72%, $p \leq 0.05$). Dose-dependent reductions in peak +dp/dt were evident in groups I, II, and III without heparin exposure and groups IV, V, and VI with heparin exposure (Fig. 5).

Oxygen extraction differed significantly (Kruskal-Wallis, $p = 0.002$) among the test groups (Table 1). Four minutes after initiation of the protamine perfusion, greater declines in a–vO_2 occurred in groups III (−53%, $p \leq 0.01$) and VI (−55%, $p \leq 0.01$), compared to groups I (−25%, $p \leq 0.01$), II (−15%, $p \leq 0.05$), IV (−48%, $p \leq 0.01$), and V (−15%). Significant differences also were found follow-

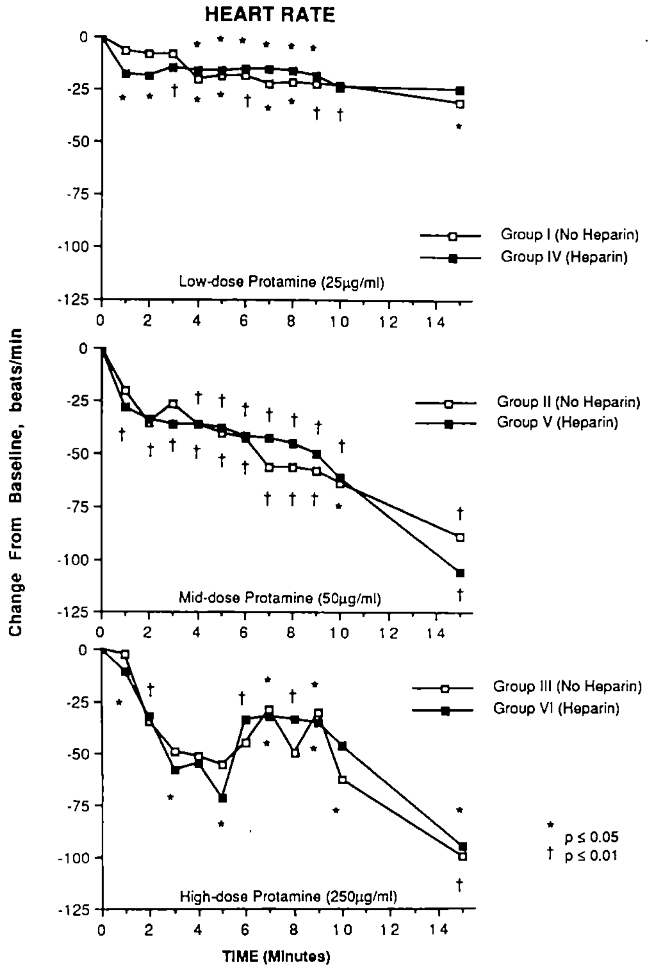

FIG. 3. Change in heart rate, groups I, II, and III with no heparin and groups IV, V, and VI with heparin, 0.1 IU/1.0 μg protamine.

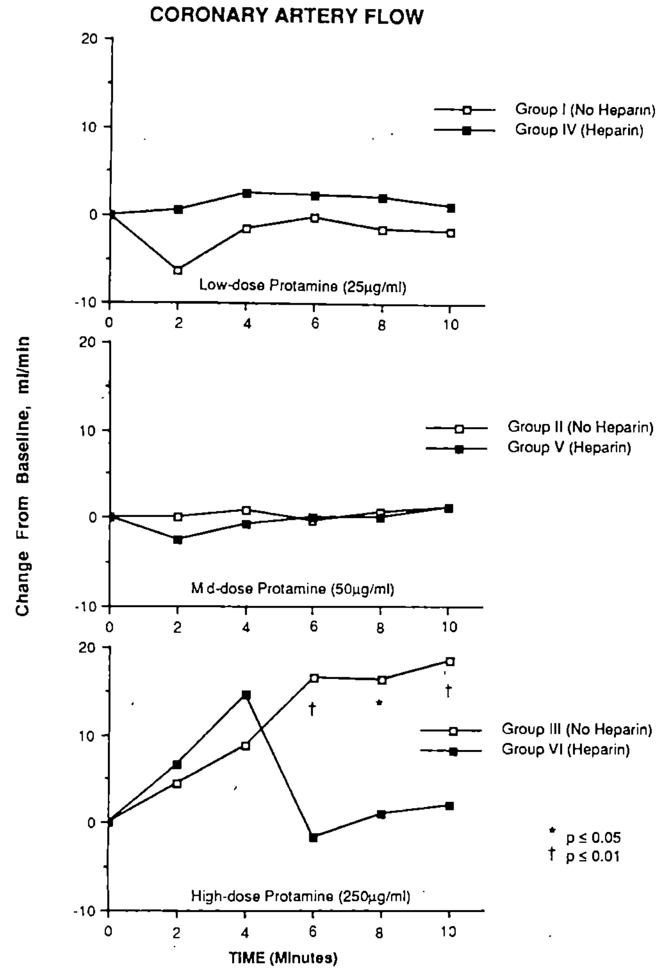

FIG. 4. Change in coronary artery flow, groups I, II, and III with no heparin and groups IV, V, and VI with heparin, 0.1 IU/1.0 μg protamine.

ing protamine exposure at 2 minutes ($p = 0.009$), 6 minutes ($p = 0.004$), 8 minutes ($p = 0.002$), and 10 minutes ($p = 0.004$). Maximum declines in a–vO_2 compared to baseline over the first 10 minutes of protamine exposure (Table 2) were group I (−31%, $p \leq 0.01$), group II (−26%, $p \leq 0.05$), group III (−79%, $p \leq 0.01$), group IV (−52%, $p \leq 0.01$), group V (−23%), and group VI (−61%, $p \leq 0.05$). Less of a dose-dependent relationship was noted in a–vO_2 in groups I, II, and III without heparin exposure or groups IV, V, and VI with heparin exposure (Fig. 6) than was apparent in hemodynamic changes. There was a tendency for a greater decline in a–vO_2 in those hearts exposed to heparin only in the low-dose protamine group than those not exposed to heparin.

Oxygen consumption declines were greater 4 minutes after beginning the protamine perfusion (Table 1) in groups III (−44%, $p \leq 0.01$) and VI (−49%, $p \leq 0.01$) than in groups I (−26%, $p \leq 0.01$), II (−12%), and V (−18%, $p \leq 0.05$). Differences existed among the groups by Kruskal-Wallis statistics at 2 minutes ($p = 0.025$), 4 minutes ($p = 0.004$), 6 minutes ($p = 0.007$), 8 minutes ($p = 0.008$), and 10 minutes ($p = 0.014$) after protamine exposure. Maximum declines in $\dot{V}O_2$ compared to baseline during the first 10 minutes of protamine perfusion (Table 2) were group I (−33%, $p \leq 0.01$), group II (−22%), group III (−70%, $p \leq 0.01$), group IV (−54%, $p \leq 0.01$), group V (−25%), and group VI (−61%). A strict dose-dependent relationship was not evident for changes in $\dot{V}O_2$ among groups I, II, and III without heparin exposure or groups IV, V and VI with heparin exposure (Fig. 7). Again there was a tendency for a greater decline in $\dot{V}O_2$ in hearts exposed to heparin only in the low-dose protamine group than in hearts not exposed to heparin. In regard to +dp/dt, a–vO_2, and $\dot{V}O_2$ data, the same statistical significance was found when comparing absolute changes as existed with percent changes.

Discussion

Protamine sulfate is the only available agent for the reversal of heparin anticoagulation in contemporary

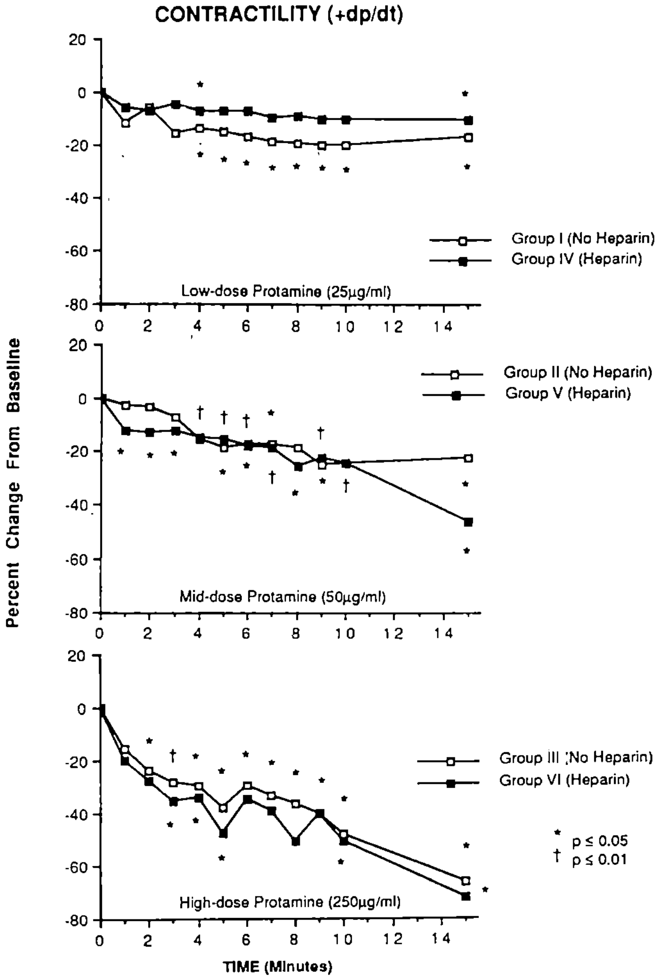

FIG. 5. Change in contractility, groups I, II, and III with no heparin and groups IV, V, and VI with heparin, 0.1 IU/1.0 μg protamine.

TABLE 1. *Changes in Oxygen Extraction (a-vO_2) and Consumption ($\dot{V}O_2$) 4 Minutes After Initiating Protamine Perfusion*

Group	Protamine Concentration in Secondary Perfusate	Heparin Concentration in Primary Perfusate	a-vO_2	$\dot{V}O_2$
I	25 μg/mL	0	−25%†	−26%†
II	50 μg/mL	0	−15%*	−12%
III	250 μg/mL	0	−53%†	−44%†
IV	25 μg/mL	0.1 IU/1.0 μg protamine	−48%†	−49%†
V	50 μg/mL	0.1 IU/1.0 μg protamine	−15%	−18%*
VI	250 μg/mL	0.1 IU/1.0 μg protamine	−55%†	−49%†

* $p \leq 0.05$ (paired t test compared to baseline). † $p \leq 0.01$ (paired t test compared to baseline).

medical practice and adverse side effects attributed to its use have become a clinical concern. These side effects include systemic hypotension, bradycardia, pulmonary artery hypertension or hypotension, thrombocytopenia, and leukopenia. In a recent report, 3% of patients receiving protamine experienced at least a 15-to-30–mmHg decrease in blood pressure, and a similar incidence of pulmonary hypertensive responses also has been documented.[10,11] The authors recently demonstrated, in a canine investigation[12] and a patient study (unpublished observations), significant declines in $\dot{V}O_2$ related to protamine administration. In the latter studies, a 55% $\dot{V}O_2$ decline occurred in dogs receiving protamine during a 10-second period, and a 16% $\dot{V}O_2$ decrease occurred in patients receiving protamine during 3 minutes to reverse their heparin anticoagulation.

It has been unclear whether the heart, pulmonary circulation, or peripheral circulation are the primary target organs for protamine's adverse side effects. Although earlier studies suggested that this drug did not have specific toxic effects on the heart,[13–15] several recent investigations suggest that protamine may cause a direct dose-dependent depression of contraction in isolated cardiac muscle strips. First, in a model studying feline papillary cardiac muscle, concentrations of protamine sulfate greater than 100 μg/mL resulted in a dose-dependent depression of all contractile parameters, delayed the onset of myofibrillar activation, and induced contracture.[16] Second, in a study involving rabbit myocardium in a tissue bath preparation subjected to varying amounts of protamine sulfate, a narrow margin in concentration between modest depression and profound depression was observed.[17] Other investigations involving human atrial appendages, acquired during coronary artery bypass procedures, demonstrated a 50% decrease in the developed force of contracture with exposure to protamine concentrations of 480 μg/mL.[18] This latter *in vitro* study revealed that high concentrations of protamine, alone or in the presence of heparin, had a direct toxic effect on human myocardial muscle mechanics. Lower concentrations of protamine, approaching 50 μg/mL, decreased isometric contraction forces by 12.4% in canine right ventricular trabeculae.[19]

It has been hypothesized that protamine causes a decline in the force of contracture by the development of slow response action potentials, occurring as a consequence of a decline in membrane potassium and sodium conductances, perhaps due to protamine's surface charge effects on membranes altering the configuration of ion channels.[23] All of the aforenoted studies demonstrated a decline in myocardial function in isolated cardiac muscle-strip preparations. The present study is the first to use a whole-organ cardiac model for the analysis of protamine's effects on the myocardium.

The present investigation established that protamine has dose- and time-specific adverse effects on cardiac function in clinically relevant amounts. In general, these adverse effects were independent of the presence or absence of heparin, suggesting that protamine itself and not

TABLE 2. *Maximum Decreases in Oxygen Extraction (a-vO_2) and Consumption ($\dot{V}O_2$) During the First 10 Minutes After Protamine Initiation*

Group	Protamine Concentration in Secondary Perfusate	Heparin Concentration in Primary Perfusate	a-vO_2	$\dot{V}O_2$
I	25 μg/mL	0	−31%†	−33%†
II	50 μg/mL	0	−26%*	−22%
III	250 μg/mL	0	−79%†	−70%†
IV	25 μg/mL	0.1 IU/1.0 μg protamine	−52%†	−54%†
V	50 μg/mL	0.1 IU/1.0 μg protamine	−23%	−25%
VI	250 μg/mL	0.1 IU/1.0 μg protamine	−61%*	−61%

* $p \leq 0.05$ (paired t test compared to baseline). † $p \leq 0.01$ (paired t test compared to baseline).

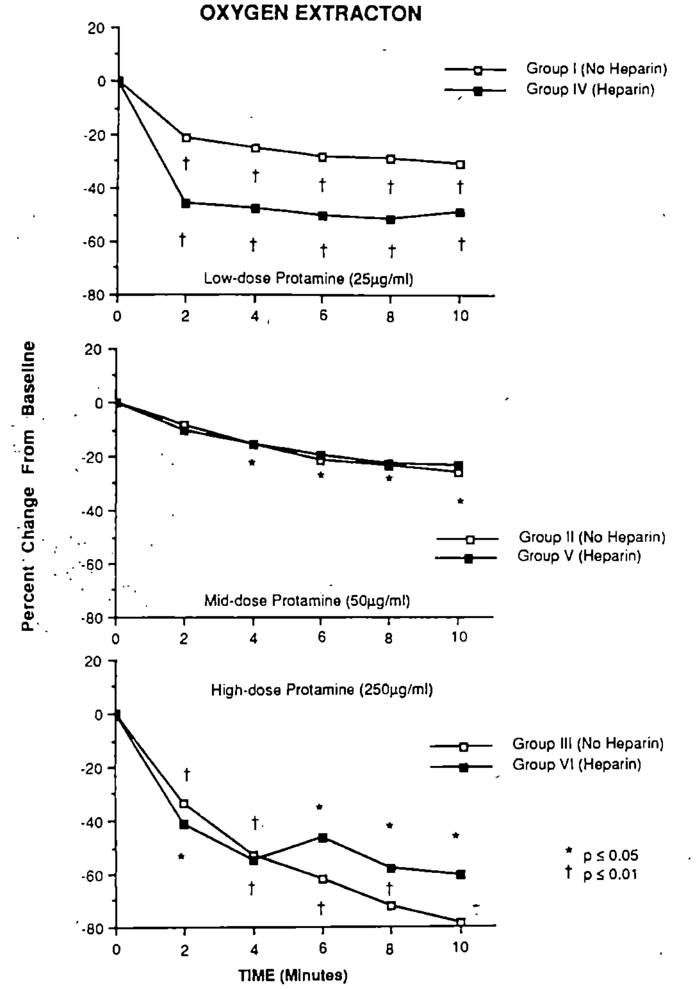

FIG. 6. Change in oxygen extraction, groups I, II, and III with no heparin and groups IV, V, and VI with heparin, 0.1 IU/1.0 µg protamine.

a protamine–heparin complex is responsible for these changes. A strict dose-dependent relationship was noted for all the hemodynamic parameters investigated. A dose of 25 µg/mL of protamine in perfusate is equivalent to a 1.5 mg/kg clinical dose of protamine, assuming equal distribution throughout the blood volume, although it has been suggested that protamine lung concentrations may be five times those concentrations occurring in the subcutaneous tissue.[24] It is particularly interesting that the HR effects were noted in this isolated preparation, in that HR changes were thought previously to reflect primarily a response to other hemodynamic events.

The declines in oxygen dynamics most likely relate to changes in mitochondrial respiration. Such effects are distinct from the hemodynamic changes, as demonstrated by the lack of a tight dose-dependent relationship in the current study. Similar separation of oxygen utilization from hemodynamic parameters was shown by other work from our laboratory involving the prostacyclin analogue, iloprost.[25] This latter drug completely blocked oxygen consumption declines accompanying protamine exposure without similarly altering the hemodynamic changes. In an *in vitro* study of endothelial cells, protamine caused up to a 50% decrease in ATP production in cultured bovine endothelium in a time and dose-dependent fashion.[26] These cells exhibited progressive mitochondrial injury, including evidence of swollen cristae, extreme vacuolization, and eventual disruption. Such cellular phenomena may explain the changes in $\dot{V}O_2$ noted in the present study. Others have noted that low concentrations of protamine stimulated mitochondrial respiration but impaired the respiratory control index, suggesting an abnormality in the proton gradient across the mitochondrial cristae, thus causing functional energy uncoupling. Protamine at higher concentrations completely removed cytochrome *c* from the inner membranes of the mitochondrial cristae, causing a total shutdown of cellular respiration.[27–32]

In the only two studies to examine oxygen consumption dynamics clinically, a 17% decrease in cardiac oxygen consumption was noted in patients given protamine at

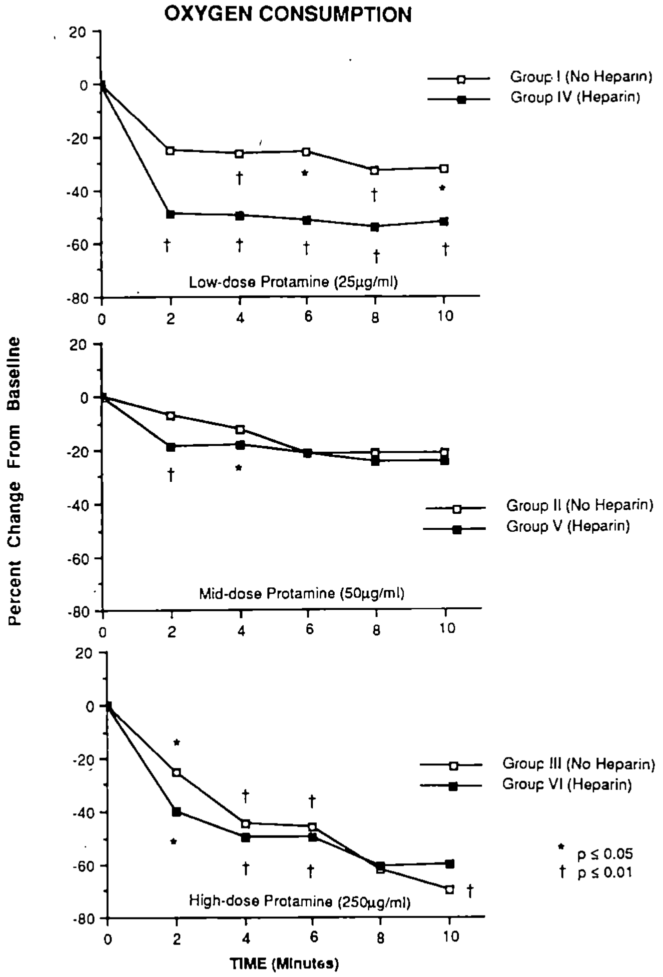

FIG. 7. Change in oxygen consumption, groups I, II, and III, with no heparin and groups IV, V, and VI with heparin, 0.1 IU/1.0 µg protamine.

the conclusion of cardiopulmonary bypass,[33] while at the authors' institution, a 16% decrease in whole-body oxygen consumption was documented in patients given protamine at the conclusion of aortic aneurysmectomy procedures (unpublished observations). The present investigation does not exclude other factors contributing to protamine's adverse side effects, such as peripheral vasodilation and sequestration of blood elements, including platelets and white blood cells. However the present study does support the tenet that cardiac responses are important in contributing to protamine's effects, and are not dependent on the presence of platelets or white blood cells. The heart appears to be an important target organ for protamine. Further studies evaluating methods to prevent or reverse the adverse cardiac effects of protamine are clearly warranted.

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DISCUSSION

DR. DONALD SILVER (Columbia, Missouri): Dr. Wakefield and his collaborators have been involved in a series of studies directed toward elucidating the mechanisms of the adverse cardiovascular and pulmonary effects occasionally seen after infusions of protamine.

The study just presented used a nicely developed whole isolated perfused rabbit heart model to assess the effects of protamine on cardiac function and metabolism. At four minutes, ventricular pressures, heart rate, and coronary blood flow were altered, but not significantly so. However, the contractility and oxygen extraction and consumption were altered significantly by the larger doses of protamine.

The effects occurred independently of the presence or absence of heparin. One has to agree with Dr. Wakefield that the heart seems to be a target organ for protamine.

I have a few questions for Dr. Wakefield. Do you plan additional mitochondrial respiratory, *in vitro*, studies in the presence of varying amounts of protamine?

Do you plan to evaluate the effects of protamine on the intact heart of other species? It seems important to determine species variability.

Do you think the buffering action of the plasma proteins that were absent in this model would alter the protamine's effect on the heart?

In view of the short circulating half-life for heparin, do you think it is worth using protamine at all? We rarely ever neutralize heparin.

Could you speculate on the mechanisms involved? For instance, are there protamine receptors on cardiac myocytes?

What is the clinical relevance of this study? Most of the major changes that you demonstrated occurred when you perfused protamine in amounts that are much higher than those used clinically.

DR. FRANK J. VEITH (New York, New York): As you know, several years ago we reported on very serious clinical protamine reactions (J Vasc Surg 1989; 9:342). We believed that most of them were due to an allergic reaction, since they occurred in patients who had been on protamine insulin preparations.

What do you think the role of allergy is in the pathogenesis of the severe clinical protamine reactions that occur?

DR. THOMAS W. WAKEFIELD (Closing discussion): To answer the first question, yes we do intend to perform further *in vitro* studies. In fact, with HPLC we would hope to be able to measure ATP and other adenine nucleotide levels directly in this model and also look at the heart muscle with electron microscopy in a similar fashion to our isolated endothelial cell model.

This model can be modified for the use of hearts from other species, and we have plans to perform studies using an isolated canine heart model in order to link these results to our intact canine model that we have used in the past.

We have limited our usage of protamine to those cases for which we suspect that bleeding is a significant risk in the postoperative period, such as with major aortic reconstructive procedures. Certainly, I believe protamine is used by most cardiac surgeons across the country at the conclusion of cardiopulmonary bypass. Although we have decreased our usage of protamine, a need still exists for an agent that can safely reverse the anticoagulant effects of heparin for complicated cardiovascular cases.

The mechanism for the adverse responses attributed to protamine is a topic for which a number of investigators, including ourselves, are working to elucidate. It does appear that protamine is a prototype polycationic substance and polycationic substances may have detrimental effects on cells in general. Such effects may be another mechanism for cell injury seen in nature, in addition to more well-known mechanisms such as oxidant injury.

We do think that the adverse responses of protamine relate to the charge of the molecule, and if you look at all of the polycationic substances that have been tried in the past to reverse heparin, protamine has been chosen because it is the least toxic of them all. Polylysine, which is a substance very much like protamine as far as its positive charge, will cause similar cellular and metabolic effects. We believe that protamine will interact inside the cell, most likely at the level of the mitochondrial cristae, and affect the polarity of the membrane. ATPase has been found to be affected by polycationic substances preventing the rephosphorylation of ADP to ATP, so clearly I believe protamine is a prototype of a compound that may cause injury in general.

The amount of protamine that we used in our preparation at the low dose would be equivalent to a typical circulating level if one assumes that the amount that is given is equally distributed throughout the body. However, we do not know this, and it has been hypothesized in the literature that pulmonary levels of protamine may be much higher than the circulating levels when a bolus infusion is given, so it is difficult to know what the actual circulating levels are compared with those we used in our model. Clearly, at the low dose level, we found very significant changes in oxygen dynamics, suggesting that even if the levels that we give systemically in the operating room are equivalent to the low circulating level, adverse effects still occur. Finally, to answer Dr. Veith's question, yes, I believe allergic reactions do play a role in the very severe protamine responses. However I think a number of studies would suggest that protamine does have adverse effects not mediated only by an immunologic cause, and clearly in the present preparation, we are not dealing with an immunologic mechanism.

Long-term Course of Patients with Persistent Hypercalcitoninemia After Apparent Curative Primary Surgery for Medullary Thyroid Carcinoma

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Thirty-one patients with persistent hypercalcitoninemia after seemingly adequate primary operation for medullary thyroid carcinoma (MTC) were followed for a mean period of 11.9 years after operation. Ten patients had sporadic MTC and the remaining patients were members of families with multiple endocrine neoplasia (MEN)—either MEN 2A (15 patients) or MEN 2B (six patients). Overall 5- and 10-year survival rates were 90% and 86%, respectively. Only four patients died at the completion of the study: two of MTC and two of unrelated causes. Eleven patients (35.5%) underwent surgical re-exploration after demonstration of recurrent disease clinically or radiologically. In no patient did the calcitonin level return to normal after re-exploration. The presence of more than three metastatic nodes at the time of initial operation was a statistically significant ($p = 0.003$) predictor for disease recurrence. Factors approaching statistical significance were patients younger than age 35 ($p = 0.06$) and the percentage of cells in the S phase of cell division (0.07). This data supports a conservative surgical philosophy in the management of the patient with persistent hypercalcitoninemia after resection of MTC.

IMMUNOREACTIVE CALCITONIN (ICT) REMAINS an excellent, and highly sensitive, biochemical marker for both the diagnosis and follow-up of patients with medullary thyroid carcinoma (MTC). All patients with MTC occurring sporadically or as a manifestation of multiple endocrine neoplasia type 2 (MEN 2) demonstrate elevated levels of iCT. This elevation may be evident in the basal (unstimulated) state or only following stimulation (pentagastrin and/or calcium). Elevated iCT levels after seemingly adequate operation (resection of all gross tumor) for MTC is a common and vexing clinical problem. In the absence of any demonstrable disease, clinically or radiologically, how should such patients be managed? How exhaustive should localization attempts be to demonstrate recurrent or residual disease? Current suggested surgical philosophy varies worldwide from a conservative approach, with excision of demonstrable recurrent disease only, to a more radical approach, with extensive removal of nodal and soft tissue that may or may not be macroscopically abnormal.

This study was undertaken to evaluate the long-term outcome of patients with persistent hypercalcitoninemia following seemingly curative initial operation.

Methods

Patients

During the period 1970 through 1985, one hundred fifty-seven patients underwent cervical exploration for MTC at our institution. Thirty-one (19%) of these patients fulfilled the following study entry criteria:

1. Initial operation at the Mayo Clinic
2. All demonstrable disease resected at initial operation
3. Documentation of elevated postoperative iCT.

These 31 patients were followed for an average period of 11.9 postoperative years (range, 1.3 to 16.8 years). In 89% of patients follow-up was available to, or within, 1 year of the completion of the study (March 1989). Follow-up was obtained by return clinic visits, by contact with the patients, or with their current local physicians.

Calcitonin Assay

Plasma iCT was measured in a radioimmunoassay using two different anti-human calcitonin antisera.[1,2] Both

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basal- and pentagastrin-stimulated iCT were measured after operation. iCT values greater than 0.65 ng/mL (female) or 0.007 ng/mL (male) in the basal state, or greater than 0.73 ng/mL (female) or 0.182 ng/mL (male) after pentagastrin stimulation in patients were considered to be consistent with recurrent or persistent MTC.

Statistical Methods

Recurrence-free survival was estimated using the Kaplan–Meier method.[3] Log-rank tests[4] assessed the effects of discrete variables, such as total *versus* subtotal initial thyroidectomy, on survival free of recurrence. The effect of continuous variables such as age and DNA index on survival free of recurrence was assessed with the Cox proportional hazards model.[5] A multivariate analysis of recurrence was not attempted because of the small number of events. P values less than 0.05 were considered statistically significant.

Results

Clinical Data

Demographics. There were 17 male and 14 female patients, with a mean age of 38.3 years (range, 12 to 69 years). In 10 patients the tumors were thought to be sporadic. In the remaining 21 patients, MTC was a manifestation of either the MEN 2A (15 patients) or MEN 2B (6 patients) syndromes. There were no patients with familial, non-MEN, MTC.

Initial operation. Total thyroidectomy was the initial operative procedure in 25 patients (80%). Total ipsilateral lobectomy alone was performed in two patients and ipsilateral lobectomy with near-total contralateral lobectomy in the remaining four patients. Twelve patients (38.7%) had ipsilateral, and four patients had contralateral, modified neck dissections. Five patients had ipsilateral, and two patients contralateral, classical radical neck dissections. Two patients underwent simultaneous bilateral radical neck dissection. A single patient had concomitant mediastinal and cervical exploration. Six patients had no nodal tissue excised.

Pathologic study. The maximum size of the primary tumors ranged from 0.5 to 10.0 cm. Fifteen tumors (48%) measured 2 cm or less in diameter. DNA ploidy data was available for 20 patients. Of these patients 17 demonstrated a diploid, 2 a tetraploid/polypoid, and 1 an aneuploid histogram. The percentage of cells in the S- or DNA-synthesis phase varied from 3.7% to 16%, with a mean value of 10.6%.

Primary tumor status. The thyroid tumors were multicentric in 18 patients (58%), with C-cell hyperplasia present in 19%.[6] Multicentricity was present in only one (10%) of the patients with sporadic tumors, in contrast to 17 patients (80%) with multiple endocrine neoplasia. The corresponding incidence of C-cell hyperplasia was 0% and 28%, respectively. All six MEN patients with C-cell hyperplasia also showed multicentricity. Eighteen (60%) tumors were bilateral (one sporadic and 17 MEN).

Nodal metastases/local invasion. Eleven patients (36%) had ipsilateral and 8 patients (26%) had bilateral metastatically involved lymph nodes. The number of positive nodes ranged from a single node in four patients to a maximum of 22 nodes in a single patient. In three patients, the primary thyroid tumor demonstrated extrathyroidal invasion into adjacent cervical muscles or nerves.

American Joint Commission on Cancer (AJCC) Staging. Nineteen patients (60%) were found to have stage III (positive regional nodes or local invasion) disease; nine patients (30%), stage II (tumors more than 1.0 cm) disease; and only three patients (10%) had stage I (tumor ≤ 1.0 cm) disease.

Follow-up

At the termination of the study (March 1989), 27 patients (87%) were alive, while 4 patients died (2 of MTC and 2 of unrelated causes; Fig. 1). Overall 5- and 10-year survival rates were 90% and 86%, respectively. Of the 27 surviving patients, 22 had no evidence of gross disease, with the remaining five patients alive with demonstrable recurrent disease. All patients had postoperative demonstration of elevated iCT levels.

Deaths

Two patients, both with sporadic MTC, died of their original disease 24 and 31 months after initial operation. Both of these patients had regional nodal metastases and local invasion of the strap muscles at the time of their original operation (stage III disease). One patient underwent two additional cervical re-explorations for locally recurrent disease before his death. Death was due to ex-

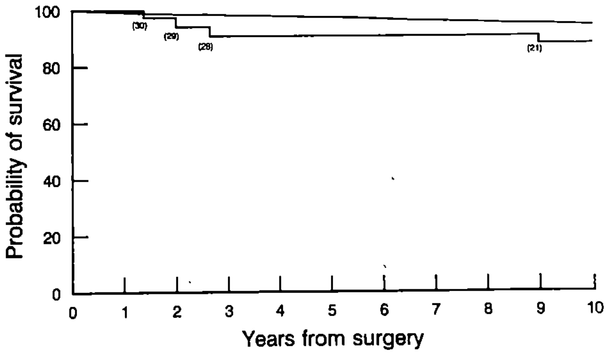

FIG. 1. Overall survival rate with expected life table survivals from North Central population.

tensive distant metastases to the liver, skeletal system, and the pericardium in both patients. Another patient (MEN 2A) succumbed to a myocardial infarction 9 years after operation, with no residual MTC demonstrable at the time of death. The final patient (MEN 2B) died 15 months after his original operation due to pulmonary complications following a bilateral radical neck dissection for bilaterally recurrent MTC.

Reoperation

Eleven patients (36%) underwent surgical re-exploration after demonstration of recurrent disease either clinically or radiologically. Twenty different surgical procedures, which included node excision, (9) node dissection, (6) mediastinal exploration, (3) excision of a subcutaneous nodule of tumor, (1) and tracheostomy, (1) were performed in this subgroup of patients. In no patient did the postoperative calcitonin level return to normal after reoperation.

Prognostic Indicators

Prognostic indicators were sought to identify those patients who might be predicted to experience macroscopic recurrent disease. Recurrent disease was used as an end point because of the small number of deaths during the study period. The 5-year probability of remaining free of gross recurrence was 61% (Fig. 2).

MEN association (p = 0.19), total *versus* subtotal initial thyroidectomy (p = 0.49), type of initial nodal dissection (modified radical: p = 0.57, or classical radical: p = 0.17), initial nodal dissection *versus* none (p = 0.47), positive *versus* negative regional nodes (p = 0.51), presence of local invasion (p = 0.24), AJCC staging (p = 0.88), tumor multicentricity (p = 0.84), tumor bilaterality (p = 0.68), tumor size (p = 0.55), DNA index (p = 0.43), and DNA ploidy pattern (p = 0.60) were evaluated and found to be of no statistical significance. Of borderline significance were patient age (p = 0.06) and percentage S phase determined by flow cytometry (p = 0.07).

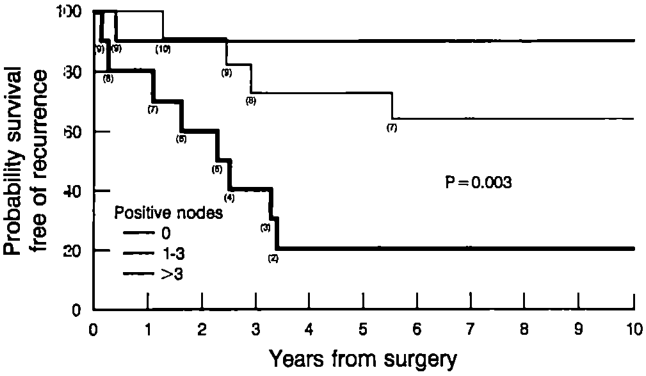

FIG. 3. Survival free of recurrence by number of positive nodes.

The 'regional node patients' were arbitrarily divided into three subgroups: (A) no nodes, (B) 1 to 3 nodes, and (C) more than 3 nodes. This division was statistically significant (p = 0.003; Fig. 3). The fact that patients with 1 to 3 nodes fared better than those with no nodes seems to be a statistical aberration. In addition, because the younger patients appeared to have a better prognosis, we evaluated the survival, free of recurrence, in those patients older and younger than the age of 35 years. This difference, however, did not achieve statistical significance (p = 0.06; Fig. 4).

Discussion

In 1962 Copp and coworkers[6] discovered a hypocalcemic factor in dogs that they named calcitonin. Erroneously they initially thought that this agent arose from the parathyroid glands *per se*. Later experiments[7] confirmed the thyroid origin of calcitonin. Today the radioimmunoassay of this polypeptide hormone probably represents one of the most clinically reliable blood tests available for diagnosing a specific type of cancer.[1,8,9] The ready availability of this sensitive marker has aided not only in the follow-up of patients after treatment of MTC but also in the earlier diagnosis of the disease.

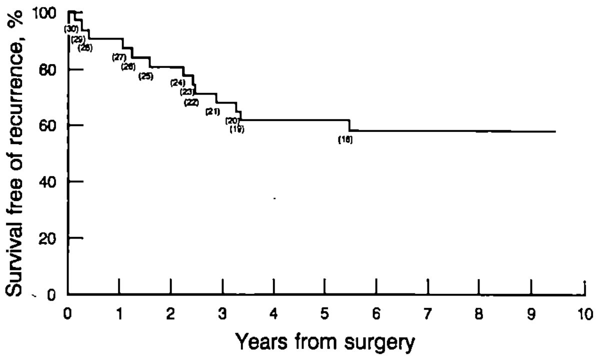

FIG. 2. Kaplan-Meier estimate of survival free of recurrence.

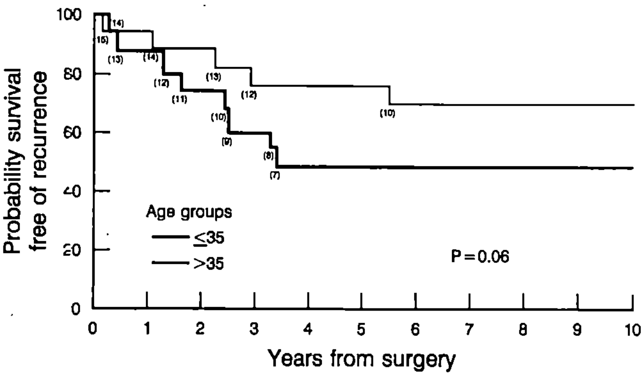

FIG. 4. Survival free of recurrence by age group.

MTC may occur in one of four distinct circumstances:

(1) Sporadically
(2) As a manifestation of multiple endocrine neoplasia type 2A syndrome (MEN 2A)
(3) As a manifestation of multiple endocrine neoplasia type 2B syndrome (MEN 2B), or
(4) In a familial, non-MEN form.

It is in the familial and MEN syndromes that the determination of iCT is of particular value. It has been demonstrated[10–13] clearly that familial screening results in the diagnosis of the disease at an earlier stage which, in turn, translates into an improvement in prognosis. Sizemore[12] emphasized that iCT measurement used in the comparison of sporadic to familial MTC resulted in an earlier age of diagnosis (27 *versus* 51 years), fewer thyroid-related symptoms or signs (33% *versus* 71%), and a lower incidence of regional metastases (23% *versus* 53%). Both Brunt[14] and Sizemore[9] emphasized that the principal prognostic markers (besides the ominous presence of clinically demonstrable disease) currently available for the management of MTC patients are calcitonin, carcinoembryonic antigen (CEA), immunohistochemical staining properties, and abnormal tumor DNA content.

Calcitonin

Not only the presence but also the actual level of basal and stimulated values are important. Although Wells[14] suggested that the levels of iCT following stimulation had a direct relationship to prognosis, Trump[15] emphasized the discordance between levels of iCT and tumor cell mass and suggested that those patients with low iCT levels and a large tumor mass may have a poor prognosis. Miyauchi[2] found that preoperative iCT levels had no correlation with prognosis and postoperative iCT levels only a weak correlation.

Carcinoembryonic Antigen

It was shown that patients with elevated levels of CEA were more likely to have metastases than those with normal CEA levels, and that there may be a rise in CEA levels without a concomitant rise in CT levels in patients with progressive disease.[16]

Immunohistochemical Staining Properties

Those patients demonstrating an intense and homogeneous stain for CT tended to fare better than did those with a heterogeneous staining pattern.[17]

Abnormal Tumor DNA Content

The adverse prognostic impact of nondiploid DNA content has been shown clearly in slide and flow cytometric studies of patients with MTC.[18,19]

These facts led Sizemore[9] to recommend aggressive therapy in those patients with low iCT immunostaining and rapid CEA doubling times.

There is no controversy regarding the optimal initial surgical treatment of MTC. Total thyroidectomy with routine dissection of adjacent nodal tissue in the central compartment of the neck and sampling of lateral jugular nodes is agreed on by all authorities in this field. If metastatic nodes are found at the initial operation, modified neck dissection should be performed, and if mediastinal metastases are present, mediastinal exploration should be considered. This aggressive surgical philosophy is predicated on the disease apparently remaining localized to the cervical and upper mediastinal regions in most patients. Also neither radiation nor chemotherapy provide effective curative adjuvant therapy.

What is controversial, though, is the management of the patient who has had seemingly adequate initial surgical treatment, no demonstrable clinical or radiologic disease, but persistently elevated levels of iCT. This is not an uncommon occurrence because persistent hypercalcitonemia is present in most patients who have nodal involvement at the time of their initial operation.

When clinical examination in this situation is negative, appropriate localizing studies should be performed. It is our opinion that the initial localizing modality should be high-resolution (10 MHz) ultrasonography with liberal use of ultrasound-guided fine-needle aspiration biopsy for tissue confirmation in equivocal cases. The efficacy of this biopsy method has been demonstrated clearly.[20–21] In a recent study of 52 patients undergoing ultrasound-guided biopsy of neck masses after previous thyroid surgery, a confident diagnosis of either benign or malignant disease could be assigned to 94% of the biopsies. High-resolution ultrasonography has indeed improved our ability to identify disease that previously remained undetected. Other suggested localizing modalities include computerized tomography and/or magnetic resonance imaging,[22] thallium-technetium scintigraphy, and scanning with technetium-99-dimer-captosuccinic acid.[23–25] As would be expected on the basis of cell origin, scanning with ^{131}I has not proved to be of value.[26] More invasive technology, which has been used sometimes, has included selective arteriography and selective venous sampling with iCT assay. Selective arteriography is particularly valuable in patients with hepatic metastases, which have a 'snowstorm' appearance. However selective venous sampling demonstrating a step up of iCT across the liver may indicate metastatic disease even when arteriography, computerized tomography, ultrasonography, isotope scans, or the determination of liver enzymes are normal.[9] Some authors suggest that selective venous catheterization may be valuable in patients with occult MTC. Ben Mrad[27] and colleagues, using this modality, identified six patients with cervical disease only. Reoperation resulted in normal iCT levels in two of these patients. We have had no experience with this technique.

If recurrent disease is demonstrated in the neck alone, or if all localizing studies are negative, should repeat cervical exploration be performed? If so, how extensive should this dissection be? The standard approach to the patient with no demonstrable disease has been one of continued observation alone. The patient with demonstrable, locally recurrent disease, which is most often located in the neck, most commonly undergoes a conservative surgical procedure. This approach has, almost universally, not returned the iCT to normal levels. Block,[28] Norton,[29] and Wells[14] have reported on patients treated with this conservative surgical philosophy, and in only isolated cases the postoperative iCT levels returned to normal. Wells[14] emphasized the indolent course of even patients with stable, mildly elevated iCT levels, with all nine of the patients in his series alive at a mean interval of 8.7 years after initial thyroidectomy. An alternative, more radical surgical approach to this subgroup of patients recently has been suggested by Tisell.[30,31] Using meticulous microdissection of the neck (a mean of 65 nodes excised during an operation that took between 8 to 12 hours), nine patients have experienced a return to normal calcitonin levels after operation. There is no long-term follow-up data available on this fascinating group of patients: this will be awaited anxiously by the entire surgical community. To quote Wells, 'This is an important study because it is the first to suggest that successful eradication of all remaining foci of occult medullary thyroid carcinoma may be accomplished in some patients by meticulous reoperation.'[14]

Our results, once again, point to the often indolent course of the disease despite, at times, the presence of regional metastatic disease. Five- and ten-year survival rates were 90% and 86%, respectively, with only two patients in this study dying as a direct result of their MTC. Predictors of clinically apparent recurrence were difficult to delineate. Although the mere presence or absence of positive regional nodes was not predictive ($p = 0.51$), more than three metastatic nodes was statistically significant ($p = 0.003$). The only other prognostic indicators that approached statistical validity were the percentage of cells in the S phase of cellular division ($p = 0.07$) and patient age less than 35 years ($p = 0.06$).

With the recent localization of the specific genetic defect in multiple endocrine neoplasia (to chromosome 10), it is possible that neonatal diagnosis may become a reality in the foreseeable future.[32] We know of the excellent prognosis when MTC can be diagnosed and treated at an early, preclinical stage by routine screening, which is so vital in the familial situation. It is thus our recommendation that we should:

- Pursue genetic typing and careful screening of the kindreds in all patients with a familial syndrome.
- Perform total thyroidectomy, central nodal dissection, and lateral node sampling/dissection as the initial surgical treatment in all patients.
- Continue to use CT measurements as an integral part of the follow-up of all MTC patients to document persistent or recurrent disease.
- In the face of persistent hypercalcitoninemia, actively pursue noninvasive localization studies to identify resectable disease.

Although we advocate re-exploration in those patients with demonstrable disease, truly occult disease does exist, albeit rarely. Achieving sustained normal levels of calcitonin following the radical approach of Tisell[31] is rarely justified by the time, effort, and limited success, and more importantly, the excellent overall course of patients who are treated conservatively.

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DISCUSSION

DR. NORMAN THOMPSON (Ann Arbor, Michigan): Dr. van Heerden has focused on what he called a common and vexing problem. Indeed, it is because we are seeing more and more of these MCT patients who have had what was considered an adequate operation and no subsequent clinical but only biochemical evidence of disease. They had 31 such patients of a total of 157. This report initially gives us the impression because of a 5-year survival of 90% that this is an indolent disease causing no great problems. That may be misleading. What was the mortality rate in the other 126 patients who were treated during the same time period?

Our policy has been similar to theirs. You have heard the controversy. There is no real controversy now related to the standard operation.

All would agree that a total thyroidectomy and a central compartment node dissection are indicated. The problem in the past has been that when the more lateral lymph nodes were involved and node dissection was done, most of us never had a biochemical cure. Now we are probably getting these patients at an earlier stage and perhaps Dr. van Heerden's patients represent that group. This shows a difference in the life history of this disease in that many of these patients now live longer than we ever had thought before they develop clinical recurrences. Our current policy, when confronted with this situation, is to study the patient with noninvasive techniques initially and also do selective venous sampling to rule out liver or other distant disease. In those cases in which the disease is apparently localized to the neck, we are going back to performing dissections.

In this group we have achieved some biochemical cures. During the last 5 years we have "cured" 5 of 15 patients. We have used both thallium scans and cervical ultrasounds, which unfortunately have been positive in only about 30% of the cases. When either is positive we have then used selective venous sampling for calcitonin and if levels were localized to the neck, we have considered a neck dissection as indicated.

DR. SAMUEL WELLS (St. Louis, Missouri): The one point that I would like to make on my slide is that the early diagnosis and treatment of patients with familial medullary thyroid carcinoma is the single most important factor in assuring long-term disease-free survival. In this slide are shown data from 96 patients with familial medullary thyroid carcinoma, excluding patients with MEN-2B and, of course, patients with sporadic medullary carcinoma.

All of these patients were treated surgically by our group and followed for a mean of 8.7 years after thyroidectomy.

The master column on the left denotes preoperative stimulated plasma calcitonin levels in four categories—those with 250 to 1000 pg/mL, 1000 to 5000 pg/mL, 5000 to 10,000 pg/mL, and more than 10,000 pg/mL. The four subsequent columns denote cervical lymph node metastases, elevated postoperative calcitonin (which is the most sensitive indicator of residual or recurrent medullary thyroid carcinoma), distant metastases, and death.

We have shown previously that there is a linear, albeit somewhat rough, correlation between medullary thyroid carcinoma tumor burden and plasma calcitonin levels. These data show that the frequency of regional lymph node metastases, postoperative elevated plasma calcitonin levels, distant metastases, and death increase with increasing preoperative calcitonin levels. Most patients with large tumor burdens are incurable at the time of initial surgery. This emphasizes the importance of early screening and the continued responsibility placed on clinicians who care for pedigrees with these familial diseases.

Patients with elevated plasma calcitonin levels after operation represent a difficult management problem. Do Dr. van Heerden and his colleagues think that any patients with persistent or recurrent medullary thyroid carcinoma merit re-exploration of the neck? I think that some of these patients do.

DR. STANLEY FRIESEN (Kansas City, Missouri): I have to agree with the main thrust of the paper, which shows that patients and their persistent tumors can live together for a long time. However I hope that surgeons will not become too complacent in the follow-up of these patients (who have persistent hypercalcitonemia after operation) as a result of hearing this paper, because I think there are some patients who can be converted with a re-exploration from a positive biochemical status to a normal one.

I note in their presentation that no patients were converted to normal calcitonin levels by reoperation. The detection and localization of persistent medullary carcinoma after operation may be difficult or, sometimes, simple. For instance I have one patient with MEN-2A who had her total thyroidectomy at the Mayo Clinic for medullary carcinoma, with one involved lymph node, and whose 1-cm nodule was easily felt in the supraclavicular area after operation. I simply excised this metastatic lymph node and her calcitonin level became normal even with pentigastrin stimulation. I also carried out total thyroidectomies on those of her children who had normal calcitonin values but which were stimulated abnormally with pentigastrin. They had C-cell hyperplasia and thus were prevented from developing carcinoma. I believe this demonstrates a more aggressive approach than is represented in this paper.

DR. COURTNEY TOWNSEND (Galveston, Texas): I would like to ask about your first conclusion in the abstract. It states: This experience reconfirms the immunological harmony between tumor and host frequently encountered, et cetera.

What is the evidence that these tumors are immunogenic in humans and what immunologic mechanisms have been defined to establish that immunologic reactivity controls the growth rate of these tumors in patients?

DR. D. CRAIG MILLER (Riverside, California): I would like also to relate the history of a patient of mine who was operated on 9 years ago, a woman with sporadic disease, age 37 years, who had a preoperative serum calcitonin level of 54,000 pg/mL. She had a total thyroidectomy, lymph node dissection, modified dissection on one side with 5 of 16 nodes positive, the largest of which was 2.5 cm.

The calcitonin level decreased to 300 pg/mL after that operation and during the past 9 years has gradually increased to the 800 to 1000 pg/mL range. There has been no clinical or radiologic evidence of recurrent disease.

How should this patient be followed?

DR. HAILE DEBAS (San Francisco, California): I suspect that the cause of hypercalcitoninemia after total thyroidectomy is due to the presence of tumor somewhere in the body.

I would like to ask Dr. van Heerden, however, if he has considered another explanation. The gene for calcitonin is processed alternatively such that in the thyroid, in the C cells, it is processed to form calcitonin, whereas in neutral tissue both in the central nervous system and in the gastrointestinal tract it is processed to calcitonin gene-related peptide. This site-specific processing, however, is not always perfect, so that the thyroid may produce calcitonin gene-related peptide, while the nerves of the intestine may elaborate calcitonin.

Is it possible that in some of these patients with residual hypercalcitoninemia, the origin of their calcitonin is from nervous tissue rather than from the residual tumor?

DR. COLIN G. THOMAS, JR (Chapel Hill, North Carolina): We know that there is a relationship between the gross amount of MTC and the serum calcitonin level.

At what level should we start to evaluate these patients on a very aggressive postoperative basis?

DR. CLIVE S. GRANT (Closing discussion): Dr. Thompson, we did not specifically study the mortality rates of the remaining 126 patients. However, in a related study that we are planning to report shortly, the overall survival rate of a different group of 119 patients who were reviewed primarily to study DNA ploidy, the 5-, 10-, and 15-year survival rates were 85%, 74%, and 69%. This is a bit misleading, however, because there were many stage I patients included. If one were to separate patients in this study into stage I through IV by the AJCC staging systems, all of the patients with stage I disease were alive throughout the entire follow-up period.

In contrast, however, patients with stage III disease had 5- and 10-year survival rates of 80% and 67%, and less than 50% of those with stage IV disease even survived 5 years. The issue of whether this disease is important regarding mortality rate can be answered, absolutely yes. We didn't mean to make any implication to the contrary.

Dr. Wells is to be complimented as a leader in this field. I am sure some of you in the room remember 12 years ago when he presented important data verifying the information regarding early diagnosis that he reaffirmed today.

The question that he brought forth related to which patients merit re-exploration. We find that this involves striking a balance between aggressive dissection, with its potential attendant morbidity, as opposed to following a totally nihilistic approach in which we would not re-explore any patient. We think that the most appropriate course is one between the two extremes. We make aggressive but noninvasive efforts to investigate these patients primarily with the use of high-resolution, small parts ultrasonography. We have found it to be very helpful in finding even small amounts of disease.

When we do find evidence of node metastases, which are principally limited to the neck, we reoperate to remove them, but to our frustration, the calcitonin level never returns completely to normal.

Dr. Townsend questioned our use of the term 'immunological harmony,' and I think his point is well taken. We don't have specific evidence elucidating these immunologic mechanisms. Perhaps we should say that the 'host/tumor relationship is in harmony.'

To elaborate further on patient follow-up, we are diligent to obtain sequential serial values of immunocalcitonin and CEA. If the levels are more than minimally elevated, we investigate these patients with high-resolution ultrasound and CT scan of the mediastinum. We have not used selective venous sampling, and Dr. Thompson should be congratulated on returning his patients to a normal calcitoninemic state using this technique.

Dr. Debas raised the possibility of the calcitonin being elevated for reasons other than persistent disease. This is a fascinating idea. I would be delighted to ascribe the elevated values in our patients to something other than persistent disease, and perhaps it is true, but in this setting it seems unlikely and would be difficult to prove.

Changing Arteriosclerotic Disease Patterns and Management Strategies in Lower-limb–Threatening Ischemia

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From January 1, 1974 to December 31, 1989, we treated 2829 patients with critical lower-extremity ischemia. In the last 5 years, 13% of patients had therapeutically significant stenoses or occlusions above *and* below the groin, while 35% had them at two or three levels below the inguinal ligament. Unobstructed arterial flow to the distal half of the thigh was present in 26% of patients, and 16% had unobstructed flow to the upper third of the leg with occlusions of all three leg arteries distal to this point and reconstitution of some patent named artery in the lower leg or foot. In the last 2 years, 99% of all patients with a threatened limb and without severe organic mental syndrome or midfoot gangrene were amenable to revascularization by percutaneous transluminal angioplasty (PTA), arterial bypass, or a combination of the two, although some distal arteries used for bypass insertion were heavily diseased or isolated segments without an intact plantar arch. Limb salvage was achieved and maintained in more than 90% of recent patient cohorts, with a mean procedural mortality rate of 3.3%. Recent strategies that contributed to these results include (1) distal origin short vein grafts from the below-knee popliteal or tibial arteries to an ankle or foot artery (291 cases); (2) combined PTA and bypass (245 cases); (3) more distal PTA of popliteal and tibial artery stenoses (233 cases); (4) use of *in situ* or ectopic reversed autogenous vein for infrapopliteal bypasses, even when vein diameter was 3 to 4 mm; (5) composite-sequential femoropopliteal-distal (PTFE/vein) bypasses; (6) reintervention when a procedure thrombosed (637 cases) or was threatened by a hemodynamically significant inflow, outflow, or graft lesion (failing graft, 252 cases); (7) frequent follow-up to detect threatening lesions before graft thrombosis occurred and to permit correction of lesions by PTA (58%) or simple reoperation; and (8) unusual approaches to all infrainguinal arteries to facilitate secondary operations, despite scarring and infection. Primary major amputation rates decreased from 41% to 5% and total amputation rates decreased from 49% to 14%. Aggressive policies to save threatened limbs thus are supported.

ENORMOUS STRIDES WERE made in the treatment of arteriosclerotic lower extremity ischemia in the last 35 years. Operative techniques for bypassing or otherwise overcoming stenotic or occlusive lesions above and below the inguinal ligament have been developed and proved effective. However, when the arteriosclerotic disease process was advanced enough to produce ischemia that threatened limb viability, major amputation at the above- or below-knee level often has been deemed necessary. During the last two decades, we and a few others[1-5] aggressively have attempted revascularization in most patients whose lower extremities were threatened because of ischemic gangrene, ulceration, or rest pain and have shown that these efforts were valuable. Although this aggressive approach to limb salvage was first received with skepticism, such surgery now is accepted widely and practiced in many centers.

Although atherosclerosis is a segmental disease and although ideal candidates for operative and other endovascular treatments have hemodynamically significant lesions of large proximal arteries interspersed in an otherwise normal arterial tree, it has become apparent that many patients with limb-threatening ischemia have a different pattern of arterial disease characterized by diffuse and multilevel arterial involvement. Furthermore occlusive or stenotic lesions may be present entirely or predominantly below the lower half of the thigh or entirely below the knee. Many surgeons still think these patients have arteries that are inoperable because their disease is 'too distal' and

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involves arteries that are 'too small.' The frequency of such disease patterns is unknown.

In the present study we reviewed our last 16 years' experience with patients with lower-limb–threatening ischemia to accomplish several objectives. The first was to examine the therapeutically important patterns of arteriosclerotic lesions in these patients and to determine how frequently lesions at multiple levels above and below the inguinal ligament required treatment. The second was to determine how these patterns of disease have appeared to change over the years. These changes were apparent because it was the perception or recognition of disease patterns that changed rather than the pattern of the disease itself. These apparent patterns were reflected in the level of operative or other interventional therapy that was performed. A third objective was to determine the frequency and extent of arterial involvement that occurred only distal to the midthigh or distal to the knee. A fourth objective was to evaluate the impact of percutaneous transluminal angioplasty (PTA) on the management of this entire patient group. A fifth goal was to determine the importance of reintervention for failed (thrombosed) or failing (threatened but not thrombosed) primary arterial procedures. The sixth goal was to describe new therapeutic strategies that facilitate management of the patterns of disease and the need for reintervention that were encountered in many patients. A final purpose of this review was to evaluate the overall efficacy of treatment of these patients.

Methods

During the past 16 years (January 1, 1974 to December 31, 1989), 2829 patients on whom we had not performed a previous ipsilateral revascularization were admitted to Montefiore Medical Center with one or both lower extremities threatened by ischemia due to arteriosclerosis (Table 1). In this analysis we have included only diabetic and nondiabetic patients who had progressive or nonhealing toe, heel, foot, or leg gangrene or ulceration or severe rest pain uncontrolled by conservative treatment.[6] Excluded from this study were patients with only intermittent claudication (who comprised 2% to 5% of our patients undergoing operation or PTA) and those whose limbs were threatened because of infection and/or gangrene in association with intact major arterial circulation as indicated by palpable foot pulses and normal forefoot pulse volume recordings. Also excluded were patients with popliteal or femoral aneurysms without occlusive disease and patients whose limbs were threatened but who were treated by thromboembolectomy alone.

Patients with severe organic mental syndrome or gangrene and/or infection involving the deeper tissues of the midtarsal region of the foot were subjected to primary major amputation above or below the knee. Except for such patients, who comprised 4% of all those admitted to our institution,[1] all patients underwent arteriographic examination by the transfemoral or translumbar route. Visualization of all patent arteries from the renal arteries to the forefoot was possible in almost all patients. With this visualization more than 94% of earlier patient cohorts[1] and virtually all of more recent patients cohorts had some patent visualized arterial segment, albeit sometimes relatively isolated, which could be used in an attempted revascularization. The only exceptions were patients who had undergone previous operations or who had suffered an acute arterial occlusion. Extensive forefoot and heel gangrene, recent congestive heart failure or myocardial infarction, an incomplete plantar arch, and heavy circumferential calcification were not considered contraindications to attempting limb salvage, and successful revascularization often has been achieved in each of these circumstances.[1,7,8]

Our medical and surgical policies for treating these patients until 1981 have been detailed previously.[1] Important recent modifications include the following.

Graft Material

Until 1976 woven Dacron grafts were used for all bypass procedures above the groin or extending to the groin, and autologous vein grafts were used for all infrainguinal bypass operations. If no vein was available for the latter procedures, knitted Dacron grafts were used. From 1976 to 1987, woven Dacron was used for some aortofemoral grafts; expanded polytetrafluoroethylene (PTFE) grafts were used for some aortofemoral bypasses, all iliofemoral, axillofemoral, and femorofemoral procedures, and (until 1982) infrainguinal bypass operations if autologous vein was unavailable in the ipsilateral lower extremity. Some sick elderly patients requiring femoropopliteal bypass and those with veins that did not dilate to a diameter of more than 3.5 mm had the procedure performed with PTFE grafts, even if they had a usable ipsilateral vein. From 1978 to 1982, all patients undergoing infrainguinal bypass procedures who had usable ipsilateral autologous vein were randomized to receive either a vein or a PTFE graft.[9] Since 1982 any bypass to an infrapopliteal artery was performed with autologous vein if this was present in any of the four extremities as a single or composite graft of undiseased vein. Patency of long (more than 40 cm) reversed vein grafts less than 3.5 mm and all vein grafts less than 3.0 mm in minimal distended diameter was inferior to that of larger-diameter vein grafts.[10] From 1982 to 1985, randomization of femoropopliteal bypass grafts to PTFE or ipsilateral vein continued. Thereafter these grafts were performed preferentially with ipsilateral vein if it was present and had a minimal distended diameter 3.5 mm or greater, except in patients whose life expectancy was

TABLE 1. *Procedures Performed in 2829 Patients with First-time–Threatened Limbs During 16 Years**

Period	1						2					3					
Year	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	Total
Total patients with threatened limbs	126	115	101	137	129	151	217	203	205	208	222	190	206	226	211	182	2829
Aorta or iliac to femoral bypass	5	3	5	4	4	4	12	10	14	13	19	20	27	35	18	16	209
Axillofemoral bypass	6	6	3	25	20	17	19	14	10	13	19	12	9	12	11	12	208
Femorofemoral crossover bypass	8	10	5	24	15	16	22	20	28	23	18	25	23	32	19	19	307
Iliac PTA	0	0	0	0	2	20	31	26	45	40	53	51	55	67	47	48	485
CFA/DFA/PSFA to PA bypass	22	24	44	65	63	62	77	73	91	76	92	93	92	91	78	79	1122
SFA PTA	0	0	0	0	0	5	21	14	10	21	23	28	42	31	17	29	241
PA PTA	0	0	0	0	0	4	16	26	4	16	16	10	20	21	11	12	156
CFA/DFA/PSFA to DA bypass	10	7	8	38	19	41	43	34	49	51	42	36	34	39	41	41	533
DSFA/AK PA to DA bypass	0	1	3	6	4	8	9	9	11	20	10	13	15	18	21	23	171
BK PA to DA bypass	0	0	1	2	2	1	15	9	12	24	28	29	34	32	18	30	237
DA to DA bypass	0	0	0	0	0	0	1	2	4	2	5	7	12	8	6	7	54
DA PTA	0	0	0	0	0	3	9	8	1	0	6	8	13	10	8	11	77
Vein graft PTA	0	0	0	0	0	0	2	4	3	3	2	5	12	4	5	10	50
Sympathectomy alone	31	29	7	0	2	1	0	1	1	1	1	0	0	1	0	0	75
Primary BK/AK amputation	52	48	34	26	29	23	45	42	36	32	41	18	36	32	10	11	515
Total procedures	134	128	110	190	160	205	322	292	319	335	375	355	424	433	310	348	4440
Secondary BK/AK amputation	7	11	23	28	44	33	38	44	43	41	34	22	34	31	17	18	468

* PTA, percutaneous transluminal angioplasty; CFA, common femoral artery; DFA, deep femoral artery; PSFA, proximal half of superficial femoral artery; DSFA, distal half of superficial femoral artery; PA, popliteal artery; DA, distal (infrapopliteal) artery; AK, above knee; BK, below knee.

judged to be less than 2 to 3 years. In most patients requiring a femoropopliteal-to-infrapopliteal sequential bypass, the proximal graft was PTFE and the distal autologous vein. Since 1983 axillofemoral bypasses were performed with ringed PTFE grafts, and PTFE femoropopliteal bypasses were randomized to ringed or nonringed grafts.[11] Since 1987 bypasses originating from the aorta were performed with albumin-coated knitted Dacron or PTFE grafts. Since July 1985 all patients who had a usable ipsilateral greater saphenous vein and who required a bypass from the proximal half of the thigh to an infrapopliteal artery were randomized to receive a reversed or *in situ* vein graft.[12]

Graft Origin and Length

Increasingly during the 16 years of this study we have tried to minimize the length of infrainguinal vein bypasses by using more distal sites of origin in patients with unobstructed proximal arteries.[1,7,13] Short vein bypasses originating from the superficial femoral, deep femoral, popliteal, and infrapopliteal arteries and extending to distal arteries have become increasingly common (Table 1). If vein length was limited, we have even placed grafts below stenoses of 20% to 40% of luminal diameter provided no postbypass pressure gradient was present. If such a gradient was present, a prosthetic extension was performed to a site proximal to the stenosis. The practice of using these distal origin short vein grafts has maximized vein use, avoided dissection in scarred or infected groins, and simplified operative procedures. Although it is not a topic of this review, problems arising from progression of disease proximal to a distal origin graft have occurred in less than 5% of cases. They have almost always not caused graft thrombosis and have been managed successfully by proximal prosthetic graft extension.

Improved Arteriographic Technique

In addition to the adjuncts previously outlined,[1] arteriographic visualization of patent foot arteries has been improved in the last 8 years by using digital augmentation techniques when necessary (3% of cases). Another advance has been the routine performance of aortic arch vessel arteriography *via* a translumbar approach in patients who are possible candidates for axillofemoral bypass. Twenty-five per cent of such patients had important and unsuspected axillary or subclavian disease that could have hampered bypass inflow.[14] When this was found, alternate adequate inflow sites were used.

Ankle and Foot Arteries as Bypass Insertion Sites

With adequate arteriographic visualization, it has been possible to find inframalleolar arteries that could provide bypass outflow in patients who previously would have been deemed unreconstructible.[1,7,15,16] The dorsalis pedis and the posterior tibial artery in the foot as well as their main branches, the lateral tarsal artery, deep metatarsal arch, and the medial and lateral plantar arteries, have been used to provide successful bypass outflow, even when there was no patent plantar arch and other major pedal arteries were occluded (Fig. 1).

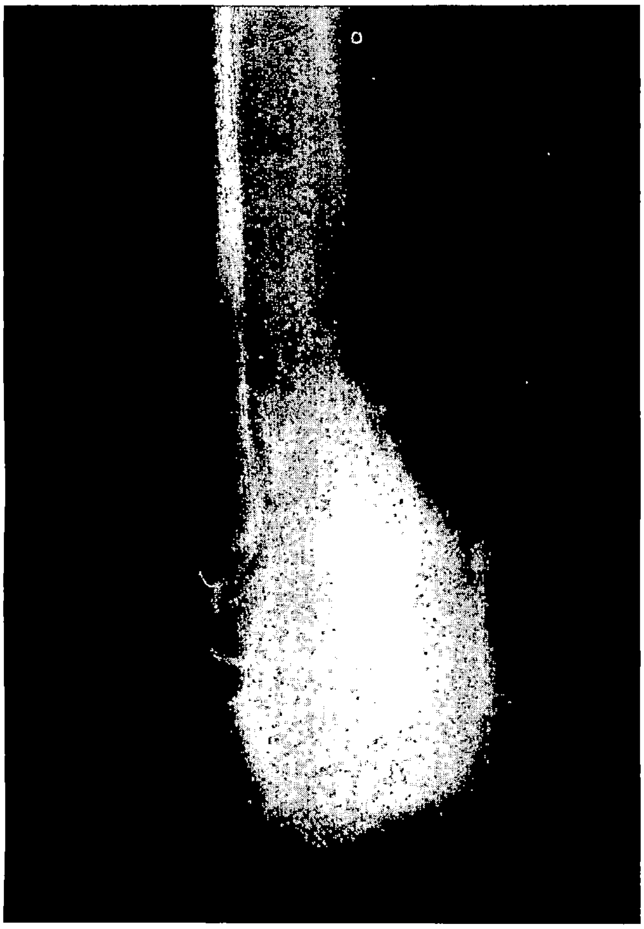

FIG. 1. Arteriogram performed 7.5 years after a below-knee popliteal-to-posterior tibial bypass. The outflow tract was limited and disadvantaged at operation and has remained so.

Use of PTA

Since 1978, if the procedure was technically feasible, we have used PTA to treat all gradient-producing or potentially gradient-producing (after distal papaverine administration) iliac artery stenoses and all potentially flow-reducing, high-grade (more than 70% reduction of luminal diameter) stenoses in the femoral arteries (common, superficial, deep) and popliteal artery.[1] If a patient with a high-grade iliac stenosis with no measurable gradient across it required an infrainguinal bypass of any sort (femorofemoral, femoropopliteal, or femoro-to-infrapopliteal), PTA of the iliac lesion also was performed.

In the last 8 years we also have extended the use of PTA with improved balloon catheters to treat stenotic lesions of the tibioperoneal trunk and the tibial or peroneal arteries at all levels in the leg, even the perimalleolar level.[17] During the last 11 years, we also have used PTA to treat lesions that have developed proximal or distal to PTFE or vein grafts and to treat stenotic lesions developing within vein grafts.[18] However intermediate (more than 1 year) results with vein graft lesions longer than 2 cm have been so poor that PTA is no longer attempted for them and vein patch angioplasty or bypass are used instead. Percutaneous transluminal angioplasty, if technically feasible, is still used for short (less than 2 cm long) vein graft lesions.

Indications for Multilevel or Sequential Bypasses

These operations consisted of axillary artery or aorta-to-femoral-to-popliteal bypasses in patients with bilateral iliac disease not amenable to PTA and femoral-to-popliteal-to-infrapopliteal artery bypasses. In the last 10 years, they were performed in one stage when extensive gangrene or infection was present in the foot and the more proximal insertion site artery ended blindly without direct luminal continuity to the lower leg or foot. In such circumstances, a simple bypass to the isolated segment would often remain patent but would not produce healing of foot lesions until a secondary distal sequential bypass was performed.[19,20] If patients had only one limb with extensive gangrene and required an axillary artery or aorta-to-femoral-to-popliteal bypass, we usually performed a unilateral procedure if the opposite limb was asymptomatic. This simplified a complicated operation, and if the opposite limb later became threatened, a simple crossover femorofemoral or femoropopliteal procedure from the unilateral prosthetic graft could be performed easily.

Postprocedural Patient Follow-up

Frequent patient observation to detect the development of flow-reducing lesions in, proximal to, or distal to the arterial reconstruction before thrombosis occurs has been important to achieving the ultimate goal of limb salvage in these patients, except for those with only an aortofemoral bypass.[1,18,21-23] Failure with thrombosis of the arterial reconstruction or PTA site can occur from intimal hyperplasia involving vein grafts, anastomotic sites, or segments treated by PTA. Usually this process becomes apparent 2 to 24 months after the arterial manipulation.[22-25] Thereafter disease progression is the most important threat to the arterial intervention. Fortunately these processes often can be detected before they cause thrombosis of an arterial reconstruction and corrective measures taken in the 'failing' state. Improved extended patency and limb salvage thus can be achieved.[18,25-27] Clinical observation with careful pulse examination by the operating surgeon every 1 to 2 months for the first postoperative year, every 3 months for the second year, and every 3 to 6 months thereafter largely has enabled us to detect 252 failing arterial reconstructions in the last 10 years (Table 2). Urgent arteriography usually was performed, and patent arterial reconstructions that were threatened were confirmed and treated by PTA (145 cases) and/or by reoperation (107 cases).

TABLE 2. *Secondary Procedures Performed for Our Failed and Failing Primary Procedures During the Last 10 Years*

Years	1980–1984	1985–1989	Total
Total number of patients with primarily threatened limb	1055	1015	2070
Number of our patients requiring a secondary procedure (% of total patients)	286 (27%)	376 (37%)	662 (32%)
Number of secondary procedures on these patients*	394	495	889
Reoperations for failed procedures (% of secondary procedures)	295 (75%)	342 (69%)	637 (72%)
Suprainguinal	47	46	93
Infrainguinal	248	296	544
Reoperations for failing procedures			
Suprainguinal	8	8	16
Infrainguinal	24	67	91
PTAs for failing procedures			
Suprainguinal	25	15	34
Infrainguinal	42	63	111
Total reinterventions for failing procedures (% of secondary procedures)	99 (25%)	153 (31%)	252 (28%)

* Many patients had more than one secondary intervention.

In the last 4 years, frequent noninvasive, Duplex examination of *in situ* vein grafts has been helpful in detecting threatening lesions before they produce graft thrombosis (graft flow velocity less than 45 cm/second).[26] Simple and effective operative intervention to improve graft patency is thereby facilitated. Accordingly we have begun to supplement clinical follow-up with Duplex examinations. However this has not always been feasible with large numbers of patients, and cost factors remain a consideration. Furthermore some grafts to disadvantaged outflow tracts have had flows less than 45 cm/second and remained patent for several years.

Management of Failed (Thrombosed) Arterial Reconstructions

Throughout the 16-year period of this review, we maintained an aggressive diagnostic and therapeutic attitude toward reintervening when a patient had a threatened limb because of failure with thrombosis of a previous arterial intervention performed at our own or some other institution.[1,24] Such patients were subjected to arteriographic examination and correction of the problem that caused or contributed to the thrombosis. In the first 10 years of this review reoperations tended to involve graft thrombectomy and salvage with patch grafting of hyperplastic outflow lesions and graft extension for progression of proximal or distal arteriosclerosis.[24] In the last 6 years, although we sometimes performed thrombectomies of prosthetic grafts terminating above the knee, we tended to perform totally new bypasses to previously undissected arteries using vein grafts where possible and a variety of new or unusual approaches to gain access to the arteries *via* unscarred and uninfected tissue planes.[28,29] Failed PTA generally was treated by a bypass, except for some focal iliac artery lesions. Not every failure of a limb salvage procedure produced a renewed threat to a limb because the original toe or foot lesion may, in part, be due to infection that never recurred. When a graft thrombosis did not threaten a limb, careful observation and expectant treatment were carried out.[24,28] Although intra-arterial lytic agents have been used sporadically in the management of thrombosed reconstructions and although they may prove helpful in the future, they were rarely valuable and not used routinely during the study period.

Management of Wound Hematoma, Necrosis, and Infection

Wound complications were frequent after infrainguinal operations in these patients, the majority (more than 60%) of whom were diabetic and who had lengthy operations with extensive vein harvest incisions. When these processes, which often occurred together, were extensive or involved more than the skin and superficial subcutaneous tissue, treatment usually involved operative debridement, evacuation of blood and exudate, and excision of all necrotic tissue. With appropriate bedside care, healing by secondary intention usually occurred, even when an autologous vein or prosthetic graft and its anastomosis to a native artery were exposed in the involved wound.[30] Skin grafts and muscle flaps were used only rarely but were helpful.

Data Maintenance and Analysis

Data for this study was culled from Vascular Service census sheets and logs of operations and PTAs. Since 1976 data on patients, their operations, PTAs, and their follow-up was entered prospectively into an IBM microcomputer relational database (Dataease International, Trumball, CT) that was specifically adopted to the monitoring of vascular patients.[31] Statistical evaluations of data were by the chi square test. The present review was performed by addressing specific queries to this database. Information on apparent disease patterns and their therapeutic significance was determined from the operations or other therapeutic interventions performed to treat the lesions deemed important. Amputation rates were derived from the number of amputations and the patients presenting primarily in the same period. Primary amputation rates minus 4% (for patients with severe organic mental syndrome and hopelessly extensive gangrene) were a reflection of untreatable arterial disease patterns. Secondary amputation rates were a reflection of early and late failures of arterial interventions that could not be salvaged by some form of secondary procedure. Although these failures and the resulting secondary amputations may have occurred remote to the arterial intervention, the overall rate calculations have validity because the number of patients treated annually remained relatively constant and eventual failures, no matter how remote, would affect the secondary amputation rate of a subsequent year if it did not increase the rate for the same year.

Results

Table 1 shows the number of patients presenting with a threatened limb from arteriosclerotic ischemia during the 16 years of the study and the therapeutic procedures performed on these patients. In the first 6 years of the study (period 1) there was a sharp rise in the number of procedures extending to infrapopliteal arteries and a corresponding decrease in the number of sympathectomies and primary amputations. This is a reflection of our increasing recognition of the therapeutic significance of infrapopliteal lesions and our increasing ability to deal with them effectively. These trends continued and increased in the latter 10 years of the study (periods 2 and 3) and were associated with the introduction of iliac and femoral artery PTAs and increasing numbers of distal origin bypass grafts and popliteal and infrapopliteal PTAs. The latter were indicative of our increasing recognition that limb-threatening ischemia could be associated mainly with distal occlusive disease below the midthigh or knee, and that these patterns of disease often occurred without therapeutically significant, more proximal disease.

Another fact that can be derived from Table 1 was the increase in the number of procedures performed per patient from 1.2 in period 1 to 1.6 in period 2 and 1.8 in period 3. This was due to our increasing inclination to treat the multiple levels of disease these patients had and our willingness to reintervene when a primary procedure thrombosed or failed to save the limb.

Changing Patterns of Therapeutically Significant or Apparent Disease

These patterns are reflected in Table 3, in which the location and number of levels of therapeutically significant disease are derived from the number of threatened limbs that received a particular treatment or had an operation or PTA to overcome a significant arterial lesion. Of the patients undergoing therapeutic arterial procedures, the proportions with therapeutically significant disease above and below the inguinal ligament did not change significantly in the 16 years of the study. However the proportion of patients undergoing treatment at multiple levels, either above and below or all below the groin, increased from 28% to 49%. Even the high proportions of multilevel procedures in the last 5 years of the study (44% to 51%) are misleadingly low because many patients with multilevel disease often could be adequately treated by overcoming only one of several lesions in series.

From 56% to 72% (mean, 63%) of threatened limbs were associated only with therapeutically significant disease below the inguinal ligament. Almost always this oc-

TABLE 3. *Locations and Level or Levels of Therapeutically Significant Arteriosclerotic Lesions in all First-time Threatened Limbs as Determined by the Arterial Procedures Performed*

Period	1						2					3					
Year	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	Total
Total limbs threatened for first time	132	124	117	163	147	191	255	244	247	264	290	240	262	281	220	188	3365
Primary major amputation	52	48	34	26	29	23	45	42	36	32	41	18	36	32	11	10	515
Sympathectomy alone	31	29	7	0	2	1	0	1	1	1	1	0	0	1	0	0	75
Arterial procedures	54	49	78	135	118	168	210	202	210	232	249	222	226	249	209	178	2789
Suprainguinal procedures alone*	19 35%	16 33%	17 22%	33 24%	32 27%	29 17%	63 30%	53 26%	56 27%	52 22%	58 23%	63 28%	57 25%	73 29%	51 24%	41 25%	713 26%
Infrainguinal procedures alone*	32 59%	32 65%	56 72%	85 63%	75 64%	113 67%	118 56%	131 65%	132 63%	159 69%	169 68%	132 59%	141 62%	145 58%	131 63%	111 62%	1762 63%
Multilevel supra and infrainguinal procedures*	3 6%	1 2%	5 6%	17 13%	11 9%	26 15%	29 14%	18 9%	22 10%	21 9%	22 9%	27 12%	28 12%	31 12%	27 13%	26 15%	314 11%
Multilevel infrainguinal procedures*	12 22%	11 22%	16 21%	39 29%	31 26%	56 33%	59 28%	70 35%	72 34%	82 35%	85 34%	71 32%	82 36%	84 34%	80 38%	62 35%	912 33%
Total multilevel procedures	15	12	21	56	42	82	88	88	94	103	107	98	110	115	107	88	1226
% Total multilevel procedures*	28%	24%	27%	41%	36%	49%	42%	44%	45%	44%	43%	44%	49%	46%	51%	49%	44%

* Percents represent fraction of total arterial procedures in that year receiving that treatment.

TABLE 4. *Therapeutically Significant Patterns of Arteriosclerotic Lesions in 2829 patients with a First-time–Threatened Limb**

Years	Period 1 1974–1979	Period 2 1980–1984	Period 3 1985–1989
Total number of patients	759	1055	1015
Number treated by sympathectomy alone (%)	70 (92%)	4 (0.4%)	1 (0.1%)
Number treated by primary major amputation (%)	212 (28%)	196 (19%)	107 (11%)
Number treated by operation or PTA for aortolliac lesion (%)	146 (19%)	252 (24%)	252 (25%)
Number treated by operation or PTA for superficial femoral and popliteal artery lesions (%)	238 (31%)	374 (35%)	336 (33%)
Number treated by operation or PTA for infrapopliteal artery lesions (%)	98 (13%)	229 (22%)	320 (32%)

* When patients treated by sympathectomy and primary amputation were excluded, the initial arterial intervention indicated the pattern of arteriosclerotic lesions. Arterial interventions were classified on the basis of the most proximal lesion treated, except for the group undergoing treatment of infrapopliteal artery lesions. Many of these latter patients also had treatment for lesions of the superficial femoral and proximal popliteal arteries. PTA, Percutaneous transluminal angioplasty.

curred at two or more levels, although only 21% to 38% (mean, 33%) required a therapeutic procedure for at least two of these infrainguinal levels of disease. Another 2% to 15% (mean, 11%) of threatened limbs were associated with suprainguinal and infrainguinal lesions, which both required interventional treatment.

Table 4 summarizes data for the three time periods on numbers and percentages of patients who had sympathectomy, primary amputation, or initial therapeutic interventions at various levels of the arterial tree. The groups treated by arterial procedures reflect the predominant patterns of therapeutically significant arteriosclerotic lesions, although these data do not stratify for single-level and multilevel lesions requiring treatment. The most striking change in the therapeutically significant disease patterns in these patients was the increase in the proportion receiving treatment of infrapopliteal artery lesions. This increased from 13% in the first period to 32% in the latter period ($p < 0.001$). Because there was a concomitant decrease in the proportion of patients treated by primary amputation and sympathectomy, it is probable that many of these latter patients in the earlier periods could have been better treated by an intervention extending to the infrapopliteal arteries. However the significance of their distal disease was unrecognized and often techniques and strategies for dealing with it were not yet developed.

Table 5 summarizes for the three periods the increasing frequency of recognized therapeutically significant disease restricted to the arterial tree distal to the midthigh and distal to the knee joint. More than one fourth of our patients in the last 5 years were recognized to have these distal disease patterns. Undoubtedly many other patients, in the early periods of the study, had similar patterns of disease, although they were not recognized. Many of these patients probably were treated less effectively by sympathectomy and amputation.

Impact of PTA

Table 6 shows that 34% of all 2221 patients presenting for the first time with a threatened limb in the last 11 years were treated by PTA. However only 19% (or 426 patients) had PTA alone. The remaining 15% (or 331 patients) of the total had a PTA and an operation. Usually this was for another lesion proximal or distal to the one treated by PTA. However in 11% (or 86) of patients treated with PTA, the operation was because the PTA had a complication or failed.

Secondary Procedures

Secondary interventions performed for failed or failing previous procedures in the latter two 5-year periods are recorded in Table 2. Of all patients treated in those 10 years, 32% required a secondary procedure. Reoperations for failed or thrombosed procedures comprised 72% of the secondary procedures, while 28% of the secondary

TABLE 5. *Numbers and Percentages of First-time–Threatened Limb Patients who Had Therapeutically Significant Disease Only Distal to the Midthigh or the Knee Joint, as Indicated by the Performance of Therapeutic Procedures Only Distal to These Levels*

Years	Period 1 1974–1979	Period 2 1980–1984	Period 3 1985–1989
Total number of patients	759	1055	1015
Number treated with operation or PTA only distal to midthigh (%)	8 (1.1%)	182 (17%)	262 (26%)
Number treated with operation or PTA only distal to knee joint (%)	6 (0.8%)	107 (10%)	160 (16%)

PTA, percutaneous transluminal angioplasty.

TABLE 6. *Role of PTA in Treating Patients Presenting for the First Time with a Threatened Limb from January 1, 1979 to December 31, 1989**

	Number			Percent of All Patients	Percentage of PTA-treated Patients
Total patients	2221			100%	—
Total patients treated by PTA	757			34%	100%
Total patients treated by PTA alone	426			19%	56%.
Iliac arteries		347			
SFA/PA		342			
DA		72			
Deaths/%		4/0.9%			
Total patients treated by PTA and operation	331			15%	44%
Proximal to bypass		184		8%	24%
Iliac arteries			136		
SFA/PA			48		
In or distal to bypass		61		3%	8%
SFA/PA/DA			11		
Vein graft			50		
For PTA complication or failure		86		4%	11%
Iliac arteries			36		
SFA/PA			36		
DA			14		

* PTA, percutaneous transluminal angioplasty; SFA, superficial femoral artery; PA, popliteal artery; DA, infrapopliteal artery. Patients having PTA alone often had lesions treated at several levels.

procedures (either reoperation or PTA) were performed for failing or threatened but unthrombosed previous interventions. The total number of secondary procedures and the proportion for failing interventions increased significantly ($p < 0.001$) in the most recent 5-year period.

Mortality, Failures, and Amputations

Table 7 lists the proportion of prosthetic grafts and the 30-day mortality, failure (thrombosis), and major amputation rates for the various surgical procedures during the last 5 years. The overall 30-day mortality rate was 3.3%, the failure rate was 4.1%, and the major amputation rate was 2.4%. The procedural mortality rate for PTA alone during an 11-year period was 0.9% (Table 6).

Major Amputation Rates

Overall major primary, secondary, and total amputation rates for the entire 16 years of the study are shown in Figure 2. The gradual decrease in total amputation rates from 49% to 14% is highly significant ($p < 0.001$) and reflects overall improvement in the treatment of this disease process. The gradual decrease in the primary amputation rate from 41% to 5% is also highly significant ($p < 0.001$) and approaches the 4% of our patients who are subjected to primary amputation because of extensive midfoot infection or necrosis or severe organic mental syndrome. This means that few recent patients (less than 1%) were undergoing primary amputation because of arterial disease that was deemed impossible to treat. The decrease in the secondary amputation rate after 1978 from 28% to 9% also was significant ($p < 0.001$). It means that more aggressive arterial interventions and increasing operability were providing durable limb salvage and not merely delaying amputation by converting primary major amputations to secondary ones.

Discussion

This review of 16 years' experience with patients who have lower-limb–threatening ischemia from infrarenal arteriosclerosis establishes several facts and raises several questions. Patients who present with this problem generally have diffuse, multilevel disease that often requires treatment by PTA or bypass procedures above and below the inguinal ligament or at multiple levels below the groin to save the limb. Furthermore the occlusive or stenotic disease process involves infrapopliteal arteries in at least one third of these patients and in about one fourth it involves the arterial tree predominantly below the midthigh or knee. Although patterns of arteriosclerotic disease in the lower extremity have been studied for many years and the frequency of distal popliteal and infrapopliteal disease appreciated,[32] only recently has the therapeutic significance of this distal disease been realized and methods developed for visualizing it arteriographically and treating it with a high degree of success. Recognition of the importance of distal disease and development of effective techniques for overcoming it have contributed importantly to recent improved operability rates and declining primary amputation rates. In the last few years, less than 1% of patients who had threatened limbs and had not been invasively treated before had patterns of arterial disease that were unsuitable for some attempt at revas-

TABLE 7. *Operative Procedures Initially Performed for Threatened Limbs in the Last 5 Years (January 1, 1985 to December 31, 1989) and 30-day Mortality, Failure, and Amputation Rates**

Operation	Number Performed	Percentage of Prosthetic Grafts	30-day Mortality Rate (%)	30-day Failure Rate (%)	30-day Major Amputation Rate (%)
Aorta or iliac to femoral bypass	116	100	2	2	1
Axillofemoral bypass	56	100	6	4	2
Femorofemoral bypass	118	100	2	3	1
Femoropopliteal bypass	433	42	3	4	2
Femorotibial/peroneal bypass	191	16	4	5	4
Popliteal or tibial to tibial/ peroneal bypass	233	4	3	4	4
Total	1147	44	3.3	4.1	2.4

* When multilevel lesions were treated, the operation performed for the most proximal lesion was the one included in this table.

cularization. Although our data document a progressive increase in the proportion of therapeutic procedures to overcome multilevel and distal arteriosclerotic lesions (Tables 1 and 3), these changes in treatment do not indicate that the actual pattern of the disease is changing, but rather that our perception or recognition of its therapeutic significance is changing.

Opinions diverge about the frequency of predominantly infrainguinal disease and that mainly or only below the midthigh and knee. Although our review suggests that these therapeutically significant patterns of disease are common (Tables 3 to 5), we may be seeing a selected population of patients with a misleadingly high incidence of predominantly infrainguinal and distal disease. This can be determined only when data from other centers becomes available. Similar confirmation of the high incidence of multilevel disease in limb salvage patients also should be sought. However our therapeutically derived data (Table 3) tends to underestimate the frequency of multilevel disease because many hemodynamically significant lesions were present in our patients but did not require treatment to save the involved limb.

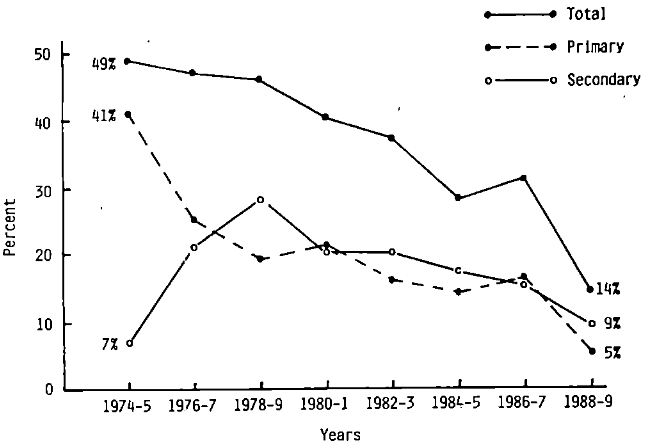

FIG. 2. Amputation rates in all patients with threatened limbs. Primary amputations were those at the above-knee or below-knee levels without previous vascular interventions. Secondary amputations were major amputations performed any time after an arterial intervention. Total amputations were all major amputations.

Our review underscores the importance of careful follow-up of limb salvage patients with reintervention if an initial procedure thromboses and fails and the limb is rethreatened. Such secondary procedures are worthwhile in terms of enhanced limb salvage.[1,24,25,27] Even more important is reintervention for a failing graft, which is not yet thrombosed but is threatened because of intimal hyperplasia or progressive disease in its inflow or outflow tract or in the graft itself.[18,21-27] Even though the need for some secondary procedures may be reduced due to improving surgical management, the number remains high (Table 2). This indicates that secondary treatment of disease progression and other problems and failures of primary procedures remain an important part of the management of these patients and one that must be pursued diligently if the optimal limb salvage results are to be achieved.

In situ vein graft techniques have been credited with much of the improvement that has occurred in the management of patients with threatened lower limbs.[33] We believe that this is true but not because *in situ* vein grafts have been proved to have better patency than reversed vein grafts.[34] As *in situ* techniques have become popular, they have led to more widespread use of careful microtechniques using special instruments, headlight illumination, and sometimes loupe magnification, all methods we have used and advocated for many years.[1,35] When such methods are used with reversed vein grafts, excellent results also can be obtained even in disadvantaged circumstances.[7,34] Furthermore *in situ* techniques are not feasible in many patients requiring a secondary operation, while use of an ectopic reversed vein graft is. Thus it is important that vascular surgeons not restrict themselves to *in situ* techniques.

Another technical modification that facilitates use of autologous vein grafts, particularly in the increasingly common group of patients requiring a secondary operation, is use of short distal origin grafts. Our data suggests that such grafts work well and have other advantages besides increasing vein use.[7,13] However proximal disease progression is a consideration, although it rarely causes graft thrombosis in our experience.

The present review demonstrates that PTA, when it was feasible in limb salvage patients, was usually a simpler, safer, often complimentary mode of therapy. In the last 10 years, 34% of our limb salvage patients were treated by PTA (Table 6). However 44% of these patients required an operation as well. Usually the operation was needed for a second lesion that could not be treated by PTA. Overall treatment thus was simplified, as has been found by others.[36] On other occasions PTA of a lesion in, proximal to, or distal to a bypass graft improved graft flow and relieved ischemia or prevented graft thrombosis. In only 11% of patients treated by PTA was an operation needed because a PTA failed or had a complication. Usually these latter operations, although more urgent, were the same or only slightly more complex than the operation that would have been required had the PTA not been attempted.[37] Furthermore when PTAs failed early or late, reintervention, usually by operation, almost always was possible. Therefore we remain enthusiastic about PTA when it is feasible in this group of patients. It is more an adjunct and aid to the surgical treatment than a competing mode of therapy. This may not be true with other forms of endovascular treatment by lasers, stents, and atherectomy devices, but this must be determined. It is not true in the treatment of patients with intermittent claudication, who generally have easier lesions to treat within a less diseased arterial tree. If treatment is warranted in such patients, it may be accomplished more safely by endovascular means alone than by open operation. However this remains to be proved, and the long-term risks and benefits of these treatments have yet to be determined. Until they are determined, we believe that patients with arterial lesions that are easy to treat generally do not need treatment. In contrast the limb salvage patients, who clearly need improved circulation but are difficult to treat by any interventional method, should be treated by whatever method proves safest and most effective. Because of the complexity and extensive nature of their disease, some form of operative bypass treatment was required in 81% of recent limb salvage patients, although often it was simplified or facilitated by PTA. In the future other newer endovascular methods may provide additional improvements in the management of these patients.

Our previous work showed that aggressive efforts by surgeons and other medical specialists to save limbs were effective. Despite the fact that 90% of patients had attempts at limb salvage, the procedural mortality rate averaged 3%, and more than 85% of patients retained a functional limb until they died.[1] The present review provides further documentation of the effectiveness of this aggressive approach. The primary major amputation rate of 5% in the last 2 years approaches the irreducible minimum proportion of patients (4%) who have severe organic mental syndrome and extensive midfoot gangrene or infection. Furthermore the proportion of patients subjected to secondary major amputation ranged between 9% and 15% during the last 5 years. These secondary amputations resulted from final, incorrectible early or late failure of limb salvage procedures. If our extension of limb salvage efforts to additional patients with more difficult distal patterns of disease had not been successful, it would have been reflected in an increasing number and proportion of secondary amputations.

Therefore we conclude that limb salvage efforts are worthwhile and that they should be extended to mentally functional patients with all apparent patterns of arteriosclerotic disease, provided extensive gangrene or infection does not involve the midtarsal region of the foot. Although the operative and radiographic procedures required to treat many of these patients often are difficult and require skill and commitment, they are rewarded with success in most instances. The resulting outcome is beneficial both to the patient and to society.

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DISCUSSION

DR. JONATHAN TOWNE (Milwaukee, Wisconsin): To my knowledge, this is the largest series of surgically treated patients with occlusive disease of the lower extremities. The operability rate of 99% in previously unoperated patients is outstanding. We agree with the desirability of autogenous repair and the good results of grafts originating from the distal superficial femoral artery, popliteal, and in our experience, occasionally tibial vessels. We do not share the author's enthusiasm for sequential bypasses. In our experience it is rarely needed to maintain graft patency or necessary to supply sufficient arterial flow to heal foot lesions. I would ask Dr. Veith to explain his indications for doing sequential bypasses. Also, I was curious, in this series what is the incidence of diabetes and its relatively changing incidence through the years?

As one reads Dr. Veith's manuscript, I wonder if it is possible to identify a group in whom it is technically possible to do a bypass but because short-term results are not as good, primary amputation may be more desirable.

Finally, when is enough, enough? When is the reoperative vascular repair not likely to be successful, and it is better to proceed to primary amputation?

In looking at these patients, some of whom had seven operations, as listed in the manuscript, what is the deterioration of patency and limb salvage curves as one adds additional operative procedures?

DR. ROBERT P. LEATHER (Albany, New York): As you know, Dr. Veith has been an enthusiastic advocate of arterial reconstruction for the prevention of amputation, a concept that originally was popularized in the late 1950s by the late Alfred Humphreys of this society. Dr. Veith's commitment can be best characterized as aggressive, persistent, and creative based on and encouraged by the constantly improving results about which we have just heard.

However I feel compelled to suggest that the title should be changed to 'Changing Management Patterns and Strategies in the Treatment of Limb-threatening Ischemia, Due to Atherosclerosis.'

I say that because I don't believe the occlusive patterns have changed, but our perception of them has, and our confidence in carrying bypasses to evermore distal arteries has steadily increased.

Our own experience in Albany, reported to this society more than 2 years ago, supports this aggressive confidence and is reflected in an even greater proportion of bypasses to the tibial level, representing more than 50% of the 2000-plus arterial reconstructions for limb salvage in the last 10 years, or in the context of infrainguinal bypasses, two tibials for each femoral-popliteal, as in contrast to the one-to-one ratio in this report.

Although we may disagree on methodology, there is complete agreement that the commitment of the surgical team is one of the most important factors in producing optimum results, for it is a tedious, time-consuming, and often frustrating effort.

I have several questions that have already been addressed, but one that struck me was the high incidence or number of revisions, constituting more than one third of the patients operated on, with 85% of these reoperations in the infrainguinal group. Does this reflect the frequent use of prosthetic material? That is, 40% in the femoral-popliteal and 16% in the femoral-tibial level.

DR. NORMAN HERTZER (Cleveland, Ohio): Lower extremity revascularization undoubtedly is the most common type of vascular surgery performed throughout the world, and many of the technical innovations that we now take almost for granted were introduced in the Bronx by these same authors. The fact that their manuscript does not contain any late patency rates will be disappointing to some and perhaps refreshing to others, but there may be many lessons learned from a review of nearly 4500 procedures in more than 2800 patients.

I would like to focus on just two of them.

Since 1974 some form of extra-anatomic bypass was used for 515 (71%) of the 724 patients who required inflow operations for aortoiliac occlusive disease in this series. Only 209 (29%) received direct aortic reconstruction, a figure that would seem rather low in my own center and perhaps elsewhere as well.

We generally restrict the use of subcutaneous grafts to patients who have compelling risk factors or surgically hostile abdomens and, for whatever reason, who are also inappropriate candidates for the retroperitoneal approach to the aorta through the left flank.

What are the indications used by the authors for extra-anatomic bypasses in the treatment of aortoiliac occlusive disease?

My second question addresses what I consider to be one of the most important issues concerning lower-extremity revascularization today. In the presence of usable saphanous vein, can below-knee prosthetic grafting finally be considered unacceptable?

Although the content of their manuscript is otherwise encyclopedic, the Montefiore group has not touched on this critical topic. It is too important, however, to ignore.

The surgeon who, as a thoughtless matter of expediency, constructs a prosthetic graft to the distal popliteal or tibial arteries is *wrong*. Do the authors agree?

Dr. Anthony Whittemore (Boston, Massachusetts): The resurrection of some 2500 limbs is a significant achievement and it testifies to the ongoing very aggressive commitment to the management of peripheral vascular disease.

I use the 'management' advisedly because our armamentarium has become extraordinarily complex. We routinely perform more distal and innovative procedures amid a burgeoning array of endovascular instruments that are being aggressively marketed, partially developed, and less intelligently applied.

I am concerned, however, that the truly important principles that underlie the favorable trends that Dr. Veith has expressed in the manuscript may be obscured in the descriptive rhetoric presented in the absence of hard data, which really testifies to the efficacy of specific interventions that he has addressed.

Two such principles deserve emphasis, and prompt my two questions. First it is clear that we can reconstruct distal tibial perineal vessels with a variety of techniques. Autogenous vein, whether it is reversed or *in situ*, provides a 75% to 80% 5-year patency rate when carried to the inframalleolar level. Such is not the case with PTFE, however, as Dr. Hertzer noted, which both in Dr. Veith's experience and in ours, provides a quite unacceptable 12% 5-year patency rate. I'll concede, however, that there may be circumstances in which PTFE carried to the infrapopliteal level might be appropriate; I have difficulty bringing them to mind, however. I would ask the authors to clarify those circumstances in which an infrapopliteal graft is indicated.

The second important principle that finally emerged from some data we produced in 1981 demonstrated the fact that secondary intervention is worthwhile for failed vein grafts inasmuch as we can achieve sustained a 50% patency rate in limb salvage following secondary or even tertiary intervention.

An unexpected observation at that time, however, was the dramatic discrepancy that appeared between grafts that were identified as failing to thrombosis and those that were intervened after thrombosis. Grafts identified before total occlusion yield an 80% 5-year patency rate in stark contrast to the thrombosed grafts, which required initial catheter thrombectomy. The same secondary procedure yielded a miserable 20% patency rate.

Despite the adoption of several graft surveillance techniques, patients still arrive at our doorstep with occlusive grafts, and how best to manage them remains highly controversial. Would the authors reveal their thoughts regarding the optimal management of totally thrombosed primary reconstruction?

Professor Roger Greenhalgh (London, England): This paper represents the struggle during the last 15 years of a development of the methods that are now being taught by vascular surgeons. I pick on just one part of this.

Using contemporary methods, the total amputation rate has decreased in these authors' records from 49% to 14%, and during that period of time other authors without vascular subspecialty training have reported a 77% midthigh amputation rate for similar patients with critical ischemia. Dr. Veith and his colleagues did not note whether their amputation was below knee or above knee.

These excellent limb salvage results reported here have occurred despite the increasing and aging population nationally and they are reproducible in other centers; for example President Mannick's and our laboratory in London have had limb salvage rates in this range, so they can be reproduced.

But a word of caution is surely appropriate. I note the need to determine a well-defined place for primary amputation. Because of this decrease in amputation rate from 49% to 14% during the years described by the authors, does this mean that expert vascular training today leads to a lower amputation rate in some parts of the community where these surgeons are found and higher amputation rate where nonspecialists manage the patient. The definitive prospective trial has not yet taken place, and we must regard the story as only partially told.

Dr. James A. DeWeese (Rochester, New York): I do note that in the last 5 years Dr. Veith found that PTA alone had increased his ability to manage many of these patients. I also know that more recently he has been involved with laser and laser-assisted balloon angioplasty as well as the other types, and I wondered whether he has found that laser technology has been helpful in his balloon angioplasty experience.

Dr. Frank J. Veith (Closing discussion): With regard to Dr. Towne's question on sequential bypasses, we use them primarily in patients who have isolated popliteal artery segments and some defect in their vein—a not uncommon finding. The lower half of the vein and the part around the knee is frequently of poor quality in our experience, and in those cases we do a sequential bypass to the popliteal artery using a prosthetic and a vein bypass to the distal artery, particularly when the foot is extremely gangrenous and ischemic. We think that patients with severe ischemia need the straight-line blood flow to the foot for it to heal. Sometimes the distal vein will close; sometimes the proximal prosthetic will close. Some of these patients then need a secondary procedure to maintain their circulation and save the foot.

Diabetics comprise from 60% to 65% of our patients. We did not analyze it specifically in this paper, although we have in the past.

We have tried very hard over the years, using measurements of outflow resistance and other criteria, to identify a group of patients in whom we can do a primary amputation because it is not worth trying to save the foot. However we failed rather miserably in this effort. Every time we come up with a possible criterion, we find that there are exceptions to it and the patient will persuade us to try to save the leg, and we find that our procedure works. Even with high outflow resistance measurements, which we described several years ago, some patients have had very short bypass grafts to very high resistance outflow tracts and have had long-term patency. Some of the examples I showed were in this category.

When is enough, enough? That is difficult to determine. Many of the patients with multiple operations have had as many as 15 operations during a period of 18 years. However these patients do not have all the operations at one time. They will come back several times with a problem during 8 to 15 years, and each time they will have another procedure to fix the problem. Many of these patients maintain both of their limbs in a functional state. One has to see some of these patients to believe how well they do. We, therefore, think we have not been able to define what *enough* is, but we do continue to look at this question.

With regard to Dr. Leather's kind comments, we agree completely that the disease is not changing. It is merely our perception and recognition of the disease that is changing. I think we just did not know what the disease was in the early years, and certainly better arteriography which you and we have, has allowed us to recognize the very distal disease, which is quite common and also quite treatable.

There is one point I did not mention. We believe the *in situ* graft may be better in certain circumstances, particularly when the vein is long and has a small diameter. However, we are performing a randomized study to prove this.

The next question concerned revision operations during many years. Again it gets to the same point that Dr. Towne mentioned: When is enough, enough? Many of these multiple operations have been used over periods of a decade or more and in those situations we believe that they are very worthwhile.

We also think that, although in the beginning some of our reoperations were due to usage of the PTFE grafts, more and more we are seeing that reoperations are required because of progressive atherosclerosis. The latter failures in particular are not due to graft failures, but to atherosclerotic disease progression.

Dr. Hertzer, there certainly are late patency statistics that we did not put in this paper. We have most of these figures, but enough is enough, and time and space constraints kept us from including some of them. We think that the bottom line from the patient's perspective was limb salvage and that was what we were trying to take a hard look at to determine if our efforts were worthwhile.

What are the indications for extra-anatomic bypass? We don't like axillofemoral bypasses either. We think they are poor operations, and we use them probably in the same situations that you do when patients are so sick that they could not tolerate a hair cut, or when they have a previously violated or infected abdomen. Even though the axillofemoral bypass is not a good procedure, it does get us out of certain very difficult situations, and a fair percentage of them remain patent for more than 5 years.

With regard to the many points about the PTFE grafts below the knee and to small vessels, that is infrapopliteal bypasses, we still think that in patients who do not have veins that can be used as a bypass graft, PTFE grafts to the popliteal artery below the knee are worthwhile. When one has to do a PTFE graft to an infrapopliteal artery, the mid-term and late patency and limb salvage rates are worse, but, in our opinion, they are often still worthwhile.

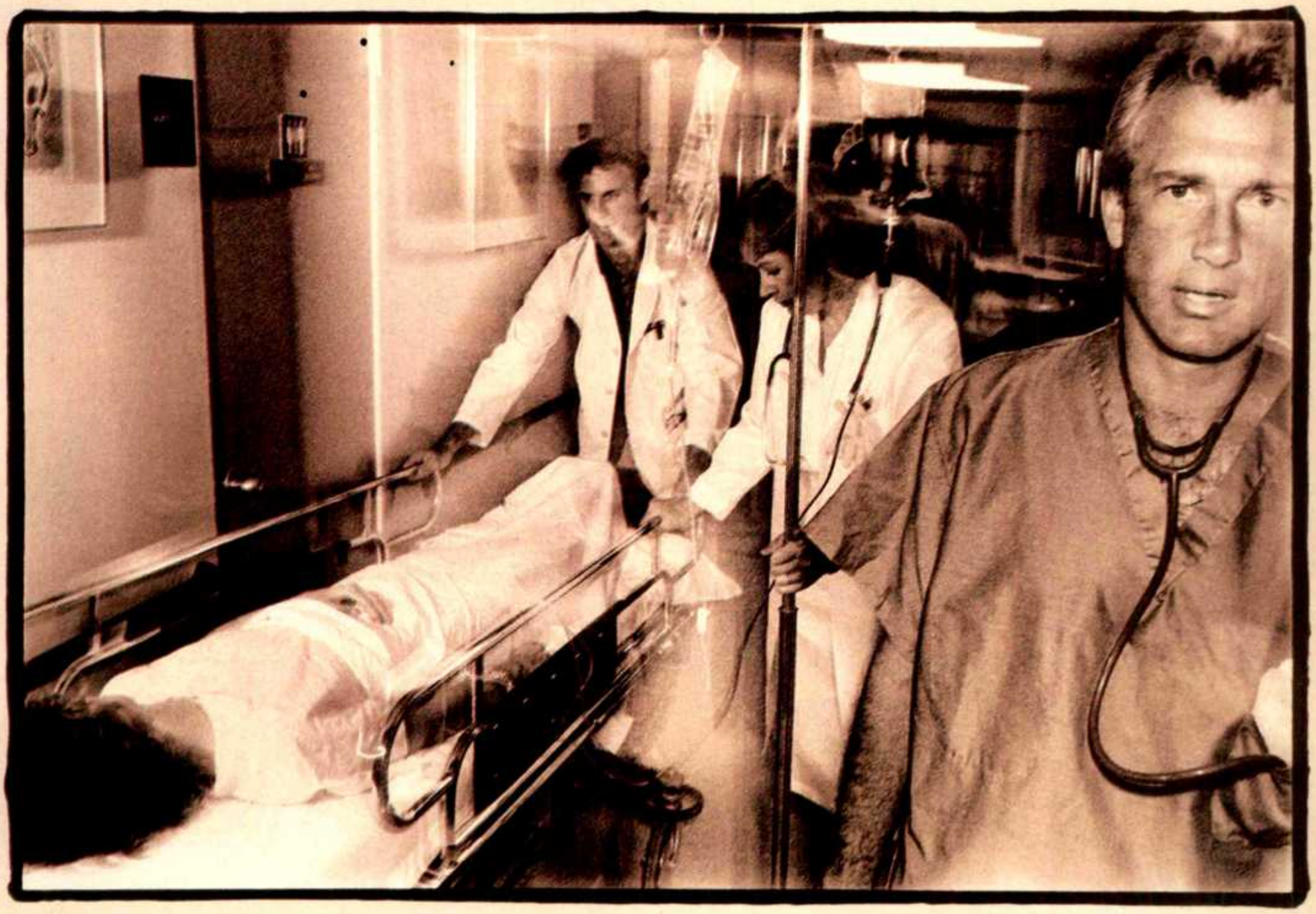
Dr. Whittemore, you also mentioned the question of small-vessel (infrapopliteal) PTFE grafts. We do not do them in patients with available vein, but we do have a fair number of patients who we characterize as 'What would they do in Portland, Oregon, or what would they do in Boston' patients. These patients truly do not have any usable veins. In such patients we still perform PTFE infrapopliteal grafts. Limb salvage has been achieved in many of these patients for several years, and some have patent PTFE bypasses to crural arteries 4 to 5 years after operation.

We agree completely with the point made about failing grafts. It is much better to detect them before they thrombose. If one reintervenes before thrombosis occurs, much higher extended patency intervals are obtained. We still use PTA for short vein graft stenoses, although there is some difference of opinion about the value of this reintervention.

What do we do for a totally thrombosed graft? We now believe the best thing to do is a totally new graft using virginal arteries. Sometimes in a patient with a groin that has been dissected many times, we will thrombectomize an old PTFE graft from below and use its proximal portion for the origin of a new distal bypass. However that is not our preferred procedure. A new graft in a new field is our preference if a patient with a failed graft requires a secondary procedure to save his or her limb.

Professor Greenhalgh, I thank you for your remarks. We certainly try to do below-knee amputations even after multiple failed bypasses. Between 80% and 90% of these attempts succeed.

With regard to Dr. DeWeese's comments, the laser has not made a major impact in our practice pattern. When we analyzed the last 600 cases that presented with limb-threatening ischemia, there were only 11 suitable for the laser. That is, they had a short (<10 cm) occlusion and we could not do a standard balloon angioplasty. Thus I believe that the laser is useful in dealing with a different disease pattern or stage than that which produces threatened limbs. The laser procedures deal mainly with patients with simple lesions, and such lesions rarely produce a threat to the limb.



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Intra-Abdominal Infections caused by beta-lactamase producing strains of *Escherichia coli*, *Klebsiella* spp. (including *K. pneumoniae**), *Bacteroides* spp. (including *B. fragilis*), and *Enterobacter* spp.*
Gynecological Infections caused by beta-lactamase producing strains of *Escherichia coli*,* and *Bacteroides* spp.* (including *B. fragilis**)
*Efficacy for this organism in this organ system was studied in fewer than 10 infections.
While UNASYN* (ampicillin sodium/sulbactam sodium) is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to treatment with UNASYN due to its ampicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and beta-lactamase producing organisms susceptible to UNASYN should not require the addition of another antibiotic.
CONTRAINDICATIONS
The use of UNASYN is contraindicated in individuals with a history of hypersensitivity reactions to any of the penicillins.
WARNINGS
SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, UNASYN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED.
SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.
PRECAUTIONS
General: A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. In patients treated with UNASYN the possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.
Drug Interactions: Probenecid decreases the renal tubular secretion of ampicillin and sulbactam. Concurrent use of probenecid with UNASYN may result in increased and prolonged blood levels of ampicillin and sulbactam. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with UNASYN and allopurinol administered concurrently. UNASYN and aminoglycosides should not be reconstituted together due to the *in vitro* inactivation of aminoglycosides by the ampicillin component of UNASYN.
Drug/Laboratory Test Interactions: Administration of UNASYN will result in high urine concentrations of ampicillin. High urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using Clinitest™, Benedict's Solution or Fehling's Solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix™ or Testape™) be used. Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriolglucuronide, conjugated estrone, and estradiol has been noted. This effect may also occur with UNASYN.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.
Pregnancy
Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to UNASYN. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. (See—Drug/Laboratory Test Interactions.)
Labor and Delivery: Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions, and duration of contractions. However, it is not known whether the use of UNASYN in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.
Nursing Mothers: Low concentrations of ampicillin and sulbactam are excreted in the milk; therefore, caution should be exercised when UNASYN is administered to a nursing woman.
Pediatric Use: The efficacy and safety of UNASYN have not been established in infants and children under the age of 12.
ADVERSE REACTIONS
UNASYN is generally well tolerated. The following adverse reactions have been reported.
Local Adverse Reactions
Pain at IM injection site—16%
Pain at IV injection site—3%
Thrombophlebitis—3%
Systemic Adverse Reactions
The most frequently reported adverse reactions were diarrhea in 3% of the patients and rash in less than 2% of the patients.
Additional systemic reactions reported in less than 1% of the patients were itching, nausea, vomiting, candidiasis, fatigue, malaise, headache, chest pain, flatulence, abdominal distension, glossitis, urine retention, dysuria, edema, facial swelling, erythema, chills, tightness in throat, substernal pain, epistaxis and mucosal bleeding.
Adverse Laboratory Changes
Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were:
Hepatic: Increased AST (SGOT), ALT (SGPT), alkaline phosphatase, and LDH.
Hematologic: Decreased hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, platelets and increased lymphocytes, monocytes, basophils, eosinophils, and platelets.
Blood Chemistry: Decreased serum albumin and total proteins.
Renal: Increased BUN and creatinine.
Urinalysis: Presence of RBC's and hyaline casts in urine.
The following adverse reactions have been reported with ampicillin-class antibiotics and can also occur with UNASYN.
Gastrointestinal: Gastritis, stomatitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis.
Hypersensitivity Reactions: Urticaria, erythema multiforme, and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with a penicillin (see WARNINGS).
Hematologic: In addition to the adverse laboratory changes listed above for UNASYN, agranulocytosis has been reported during therapy with penicillins. All of these reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

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Urinalysis: Presence of RBC's and hyaline casts in urine.

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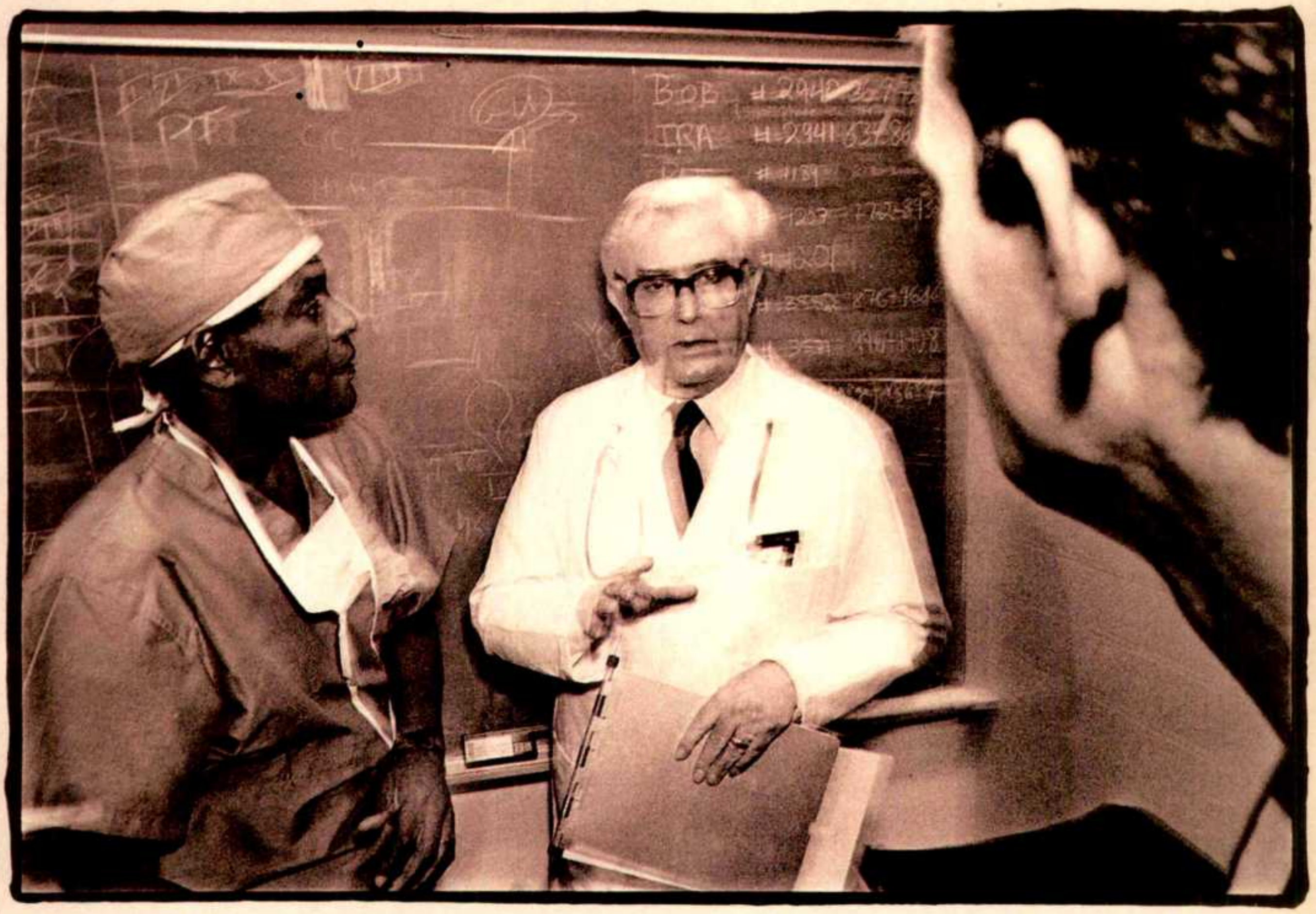

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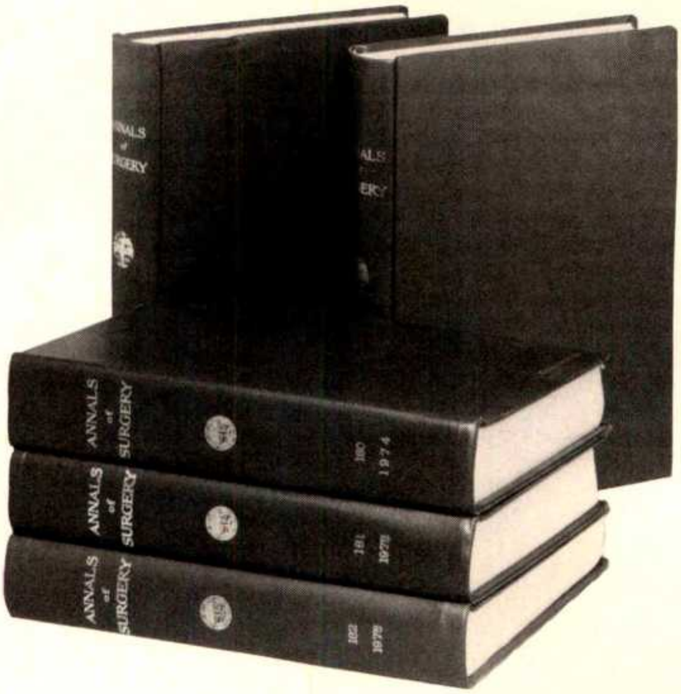

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MICHAEL A. GOLDEN, M.D., ANTHONY D. WHITTEMORE, M.D., MAGRUDER C. DONALDSON, M.D.,
and JOHN A. MANNICK, M.D.

Reduction of cardiac mortality associated with abdominal aortic aneurysm (AAA) repair remains an important goal. Five hundred consecutive urgent or elective operations for infrarenal nonruptured AAA were reviewed. Patients were divided into three groups based on preoperative cardiac status: group I ($n = 260$, 52%), no clinical or electrocardiographic (ECG) evidence of coronary artery disease (CAD); group II ($n = 212$, 42.2%), clinical or ECG evidence of CAD considered stable after further evaluation with studies such as dipyridamole-thallium scanning, echocardiography, or coronary arteriography; group III ($n = 28$, 5.6%), clinical or ECG evidence of CAD considered unstable after further evaluation. Group I had no further cardiac evaluation and groups I and II underwent AAA repair without invasive treatment of CAD. Group III underwent repair of cardiac disease before ($n = 21$) or coincident with ($n = 7$) AAA repair. In all instances, perioperative fluid volume management was based on left ventricular performance curves constructed before operation. The 30-day operative mortality rate for AAA repair in all 500 patients was 1.6% ($n = 8$). There was one (0.4%) cardiac-related operative death in group I, which was significantly less than the five (2.4%) in group II ($p < 0.02$). Total mortality for the two groups were also significantly different, with one group I death (0.4%) and seven group II deaths (3.3%), ($p < 0.02$). These data support the conclusions that (1) the leading cause of perioperative mortality in AAA repair is myocardial infarction, (2) correction of severe or unstable CAD before or coincident with AAA repair is effective in preventing operative mortality, (3) patients with known CAD should be investigated more thoroughly to identify those likely to develop perioperative myocardial ischemia so that their CAD can be corrected before AAA repair, and (4) patients with no clinical or ECG evidence of CAD rarely die of perioperative myocardial infarction, and thus selective evaluation of CAD based on clinical grounds in AAA patients is justified.

REPAIR OF ABDOMINAL aortic aneurysm (AAA) has become a safe operation in the past two decades and clearly has been shown to prolong life. However coronary artery disease (CAD) is often present in patients with AAA, and myocardial infarction (MI) is the major cause of perioperative death. To minimize the risk of cardiac mortality, some authors recommend routine preoperative coronary angiography, with coronary revascularization preceding aneurysm repair when indicated. Others have recommended routine noninvasive preoperative studies to identify patients at risk for perioperative MI. During the past 16 years, we have stratified prospectively patients with AAA into three groups before operation based on preoperative clinical evidence of CAD. Subsequent patient management was determined by this initial stratification. We now report the results of this policy in 500 consecutive patients who underwent repair of nonruptured AAA.

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Methods

Patient Population

The records of 500 consecutive patients with nonruptured, infrarenal AAAs repaired by the senior authors between 1973 and 1989 were retrospectively reviewed (Table 1). There were 94 (19%) women and 406 (81%) men, with average age 69 years (range, 42 to 94 years). The median maximal AAA diameter was 6 cm (range, 4 to 15 cm). Symptoms were present in 168 (34%) and 332 (66%) were asymptomatic. Most of the patients (86.9%) had one or more known operative risk factors, with the most common (48%) being CAD (Table 2).

Preoperative Evaluation of Cardiovascular Risk

Patients were divided into three groups based on their cardiovascular risk status (Table 3). Group I consisted of

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TABLE 1. *Patients Operated on for Abdominal Aortic Aneurysm (1973–1989)*

No. Patients	500
Male:Female	406:94
Average age (years)	69 (42–94)
AAA asymptomatic	332
AAA symptomatic	168
Median AAA diameter (cm)	6 (4–15)

260 (52%) patients with no clinical evidence of CAD, as demonstrated by the absence of symptoms and a normal ECG. Group II contained 212 (42.4%) patients who had either symptoms or ECG abnormalities suggestive of CAD, and after further cardiac evaluation were considered to have stable CAD. At the discretion of the vascular surgeon and cardiologist, the severity and stability of the CAD in most of the group II patients were determined by echocardiography, resting gaited pool ejection fraction assessment, dipyridamole-thallium imaging, exercise tolerance testing, exercise thallium imaging, holter monitoring, or coronary angiography. Group III included 28 (5.6%) patients with severe or unstable CAD, as determined by coronary angiography in addition to noninvasive evaluation. The group III patients were further stratified into two groups: (a) asymptomatic AAA (21 patients) and (b) symptomatic AAA (7 patients). Group IIIa patients with asymptomatic AAA underwent staged procedures with initial coronary artery bypass and subsequent AAA repair. Group IIIb patients with symptomatic AAA underwent combined cardiac and AAA repair.

Perioperative Management

The perioperative management of these patients has been described previously.[1] Radial artery and thermodilution pulmonary artery catheters were routinely placed for monitoring of systemic blood pressure, pulmonary capillary wedge pressure, pulmonary artery pressures, and cardiac output. Monitoring lines were inserted the evening before surgery and serial intravenous boluses of crystalloid solution were administered to assess left ventricular performance. These catheters also were used during and after operation to assist in fluid and pharmacologic therapy. Repair of the AAA was accomplished *via* the graft inclusion technique of Creech,[2] as previously described.[1] Tube grafts were placed in 66% of patients, and 34% received bifurcation grafts. Coincident with AAA repair, various secondary procedures also were performed in 83 (17%) patients (Table 4). Immediately preceding AAA repair, seven patients underwent repair of unstable cardiac disease. Nephrectomy of nonfunctioning kidneys was performed in 12 cases with associated renin-mediated hypertension. Renal artery reconstructions were performed in 23 patients. Femoral embolectomy or femoral–femoral bypass were performed in 26 patients to restore lower-extremity perfusion. The inferior mesenteric artery was reimplanted in the arterial circulation in 10 patients for prevention of intestinal ischemia. A clip was used to interrupt the inferior vena cava in two patients to prevent pulmonary emboli. Cholecystectomy was performed in six patients for chronic cholecystitis and intraoperative splenic laceration necessitated splenectomy in five patients.

TABLE 2. *Operative Risk Factors in Patients Operated on for Abdominal Aortic Aneurysm*

Risk Factor	Percentage
Coronary artery disease	48.0
Hypertension	47.6
Chronic pulmonary disease	27.4
Arrhythmia	9.7
Peripheral vascular disease	8.4
Chronic renal disease	8.4
Diabetes	8.0
Congestive heart failure	7.9
Cerebrovascular disease	7.4

TABLE 3. *Cardiac Risk Classification*

Group	Number of Patients	%	Criteria
I	260	52.0	No symptomatic or ECG evidence of CAD
II	212	42.4	Symptomatic or ECG evidence of CAD, stable
III	28	5.6	Severe, unstable CAD
IIIa	21	4.2	Asymptomatic AAA
IIIb	7	1.4	Symptomatic AAA

ECG, electrocardiographic; CAD, coronary artery disease; AAA, abdominal aortic aneurysm.

TABLE 4. *Secondary Procedures During Repair of AAA in 83 Patients*

Procedure	Number of Patients
Cardiac	
Coronary artery bypass (CABG)	5
Aortic valve replacement	1
Aortic valve replacement/CABG	1
Renal	
Nephrectomy	12
Renal artery reconstruction	23
Other vascular	
Femoral embolectomy	23
Femoral–femoral bypass	3
Reimplantation of IMA	10
Inferior vena cava clip	2
Miscellaneous	
Cholecystectomy	6
Splenectomy	5
Resection of pheochromocytoma	1
Total procedures	92

AAA, abdominal aortic aneurysm.

TABLE 5. *Postoperative Morbidity in 500 Patients Operated on for Abdominal Aortic Aneurysm*

Complication	Number of Patients	Percentage
Myocardial infarction	15	3.0
Arrhythmia	116	23.2
Renal failure	28	5.6
Pneumonia	27	5.4
Pulmonary embolus	4	0.8
Ischemic colon	3	0.6
Reoperation for hemorrhage	5	1.0

All patients were followed for complications throughout their hospitalization and as outpatients through the 30-day postoperative period. Data were analyzed for statistical significance using Fishers exact test. The 30-day operative mortality rate for the 500 patients undergoing AAA repair was 1.6% (8 deaths). Myocardial infarction resulted in 6 deaths (1.2%) and another 2 (0.4%) patients died of pulmonary emboli. The operative mortality rate was 2.3% for urgent cases and 1.2% for elective cases.

Postoperative complications, ranging from minor arrhythmias to fatal MI, occurred in 196 (39%) patients (Table 5). Electrocardiographic or cardiac isoenzymes or both revealed evidence of MI in 15 (3%) patients. Arrhythmias were noted in 116 (23%) patients, most of which were inconsequential. Pneumonia complicated the postoperative course of 27 (5.4%) patients, and renal failure requiring serious consideration or actual institution of dialysis occurred in 28 (5.6%) patients. Colon ischemia necessitating bowel resection occurred in three patients (0.6%), and reoperation for postoperative hemorrhage was required in five patients (1%).

Cardiac Risk and Operative Results

In group I only three patients suffered perioperative MI, and one of them died. This represents a 0.4% mortality rate for patients with no preoperative symptoms or ECG evidence of CAD (Table 6).

The 212 patients in group II (42.4%) were thought to have stable cardiac disease before operation. Twelve group II patients experienced a perioperative myocardial infarction, five of whom died, representing a 2.4% cardiac related mortality rate. In addition two group II patients died from pulmonary emboli, making the total group II mortality rate 3.3%. The cardiac related mortality rate was significantly higher for group II compared to group I ($p < 0.02$) patients, as was the total mortality rate for the two groups.

Among the 21 group IIIa patients treated with CABG and staged AAA repair within 6 months for unstable cardiac disease and asymptomatic AAA, there were no MIs or deaths.

The seven patients (1.4%) in group IIIb, defined as having unstable cardiac disease and symptomatic AAA, underwent urgent combined procedures with repair of the cardiac disease followed by repair of the AAA. Five patients with crescendo angina or left main CAD unresponsive to medical therapy underwent CABG and then AAA repair before chest closure. One patient, who had critical aortic stenosis, severe CAD, and a symptomatic AAA, underwent an aortic valve replacement, CABG, and then AAA repair as a combined procedure; another patient with critical aortic stenosis and a symptomatic AAA received an aortic valve replacement and repair of AAA as a combined procedure. No patient in group IIIb suffered MI or death.

Discussion

On March 29, 1951, Charles Dubost used an aortic homograft during the first successful repair of an aortic aneurysm.[3] His achievement, which added 8 years to his patient's life, stood in stark contrast with notoriously poor outcomes derived from previous methods consisting of aortic ligation, wiring, or wrapping. While subsequent availability of prosthetic grafts firmly established this approach to aneurysm repair, initial operative mortality rates approximated 20%.[4–6] Vastly improved anesthetic management and the adoption of the graft inclusion technique advocated by Creech were among several factors responsible for the subsequent decline in operative mortality rate to the 4% to 9% range reported in the early 1970s.[2,8–10] These lower mortality figures resulted primarily from significant reduction in postoperative renal and respiratory

TABLE 6. *Myocardial Infarction and Cardiac Mortality in Patients Operated on for Abdominal Aortic Aneurysm*

Postoperative Morbidity	Group I No CAD (n = 260)	Group II Stable CAD (n = 212)	Group III Unstable CAD (n = 28)	Total (n = 500)
Non Fatal MI	2	7	0	9 (1.8%)
Op mortality, cardiac	1 (0.4%)*	5 (2.4%)*	0	6 (1.2%)
Noncardiac	0	2	0	2 (0.4%)
Total	1 (0.4%)	7 (3.3%)	0	8 (1.6%)

* $p < 0.02$.

CAD, coronary artery disease; MI, myocardial infarction; Op, operative.

failure, while the incidence of cardiac complications remained virtually unchanged.[11]

Reduction in cardiac mortality rate was forthcoming in the 1970s as the physiology of declamping hypotension became better understood and monitored perioperative fluid administration more routine.[1,12–14] Sophisticated management of the compromised myocardium reduced the anticipated operative mortality rate consistently below 6% by 1980, yet the primary cause of death remained cardiac.[1,15–20]

Further reduction in operative mortality rate requires, therefore, identification of those patients with CAD at significant risk for postoperative cardiac complications. Reliable predictors would allow more vigorous investigation of high-risk individuals and guide specific management of CAD before or concurrent with aneurysm repair. Predictive methods have included clinical scoring systems and a variety of laboratory investigations.

Several clinical scoring systems have been used to assess operative risk, perhaps the most rigorous of which is the Goldman risk index, according to which poorly controlled congestive heart failure and recent myocardial infarction represent the most ominous predictors.[21,22] Although proved accurate in several series, the index criteria were developed in the late 1970s and may not accurately reflect current management of even the most severe manifestations of CAD.[23–26] Rivers et al.[27] recently documented the incidence of cardiac morbidity in a group of 30 patients undergoing peripheral vascular surgery a median of 11 days after myocardial infarction. While the Goldman risk index accurately predicted the cardiac complication rate in class II and III patients, the 33% cardiac complication rate associated with class IV patients was significantly lower than the 78% level predicted by Goldman. None of these 30 patients, however, underwent an intra-abdominal aortic repair. Similarly Lette and associates[28] examined 66 patients and found no correlation between postoperative cardiac events as predicted by any of the five clinical scoring systems investigated, including the Goldman index, Cooperman scale, Dripps score, Detsky index, and Eagles clinical markers. The patient population in the latter study also was heterogenous but included 48 vascular procedures, 67% of which required aortic cross-clamping. Thus most clinical scoring systems are probably outdated, lack risk adjustment for the specific operative procedure, and do not seem accurate for the patient with a severely impaired myocardium. Perhaps this is not surprising because silent ischemia may be just as, if not more, important than any other clinical parameter.

The exercise tolerance test, widely used to evoke evidence of myocardial ischemia, is subject to many limitations.[29–33] A significant number of vascular patients (25% to 33%) cannot complete the standard examination, which has useful predictive value only when patients achieve 75% to 85% of their predicted maximal heart rate (PMHR).[29,30,33] Unfortunately as many as 70% of patients examined cannot achieve their PMHR,[33] and even if successfully completed, the severity of CAD cannot be accurately assessed in patients with no prior cardiac history.[32] Furthermore subsequent coronary angiography in patients with significant S-T segment depression not infrequently fails to demonstrate significant CAD.[31] The exercise tolerance test therefore may provide equivocal results requiring further stratification before appropriate referral for coronary angiography.

Resting gaited pool ejection fraction (EF), as determined by radionuclide ventriculography, also is associated with equivocal findings.[34–38] Pasternack recently determined EF in 200 patients, 34% of whom underwent AAA repair.[35] Those patients with an EF less than 40% sustained a 17% incidence of perioperative myocardial infarction, significantly greater than the 3.4% incidence observed in patients with EF in excess of 40%. Other reports refute such a correlation, one of which specifically included 60 patients undergoing AAA repair.[36–38] This is perhaps not unexpected because the EF measures the efficiency of left ventricular function at one time point and may not accurately reflect the extent of CAD and associated risk of sudden coronary occlusion.

Dipyridamole-thallium imaging has been shown to correlate well with cardiac risk.[39,40] Thallium redistribution following coronary vasodilatation induced by dipyridamole accurately reflects myocardial susceptibility to postoperative events. Unfortunately the examination is not readily available in most institutions because drug supplies remain severely rationed in the United States.

These difficulties inherent in accurate stratification of patients with CAD has led to the recommendation of routine coronary angiography and preliminary coronary artery bypass grafting (CABG) when surgically reconstructable disease is identified.[41] In more than 1000 such studies in patients before elective vascular surgery, Hertzer et al.[42] found severe but operable CAD in 25% of the entire group and in 31% of those with AAA. Eighteen per cent of those with AAA had proved and operable CAD, yet no prior history of myocardial ischemia. Of the entire group, 216 patients underwent CABG and sustained a 5.3% mortality rate before vascular surgery. Of those who survived CABG, however, only one death occurred during the subsequent vascular procedure. The added risks imposed by coronary angiography and initial CABG have cast doubt on the overall benefits of this approach.[42–44] More selective use of coronary angiography is currently recommended for patients with a positive clinical history and for those asymptomatic patients who are identified on exercise tolerance testing or radionuclide imaging as high-risk individuals.[42] Although 44% of the entire group of patients with a positive clinical history had severe operable CAD by angiography, a significant 15% of patients with an entirely normal cardiac history also had severe surgically correctable coronary disease.

Because of the unreliability of clinical scoring systems, objective laboratory tests, and the expense and morbidity associated with coronary angiography, we have implemented the clinical classification system reported in this study. Some patients with AAA without clinical evidence of CAD have significant and operable CAD, as demonstrated by Hertzer et al.[42] Despite this our policy of recommending elective repair of AAA without further cardiac work-up in patients with no clinical evidence of CAD seems justified by the minimal cardiac morbidity and mortality established in our initial experience, confirmed by others since, and reaffirmed in the present report.[45–48]

Patients with unstable CAD manifest by crescendo or nocturnal angina unresponsive to medical therapy, including those associated with symptomatic aneurysms, require coronary revascularization before, or concurrent with, AAA repair. None of our patients managed in this fashion died, even among the group of patients undergoing simultaneous CABG and AAA repair. While our experience with preliminary percutaneous transluminal coronary angioplasty is very limited, this may prove to be a safe and expeditious approach for patients with symptomatic aneurysms and correctable coronary disease.

Patients with clinically evident but stable CAD, however, are at the highest risk for perioperative myocardial events. While Hertzer et al.[42] recommend routine coronary artery angiography and CABG, as indicated for this group, we support the use of a more selective policy in which the cardiac mortality rate was limited to 2.1% of patients with known CAD (groups II and III). This figure compares favorably with the 3.9% mortality rate associated with 250 aneurysm patients reported by Hertzer[42] who underwent preliminary coronary angiography and CABG as required.

Further reduction in the cardiac mortality rate may require recognition of myocardial ischemia in these group II patients with CAD. A significant number of patients with surgically correctable CAD in Hertzer's group were clinically asymptomatic.[42] Of significant myocardial ischemic events documented on ambulatory Holter monitoring of vascular surgical patients, 75% of those reported by Pasternack and nearly all of those reported in our experience were, in fact, entirely silent.[49,50] These observations challenge our ability to accurately determine the relative stability of CAD. Prospective studies using routine ambulatory Holter monitoring may allow further stratification of group II individuals and identify those most likely to sustain cardiac events and therefore most likely to benefit from coronary angiography and subsequent intervention.

In conclusion operative deaths resulting from cardiac events associated with repair of AAA has diminished markedly, yet myocardial infarction remains the leading cause of postoperative death in most series, including this one. Significant perioperative cardiac complications rarely develop in patients with no clincial or ECG evidence of coronary disease and thus they warrant no further cardiac evaluation. In contrast, in those patients with severe or unstable coronary disease, correction of the CAD before, or simultaneous with, AAA repair is required to minimize cardiac deaths. Those individuals with established but stable CAD, however, need aggressive investigation to detect those at highest risk for perioperative ischemia so their associated CAD may be corrected before elective AAA repair. The recognition of silent myocardial ischemia in such individuals may prove to be a most important aid in further reducing the operative mortality rate.

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DISCUSSION

DR. E. STANLEY CRAWFORD (Houston, Texas): These authors deserve congratulations for presenting another study of their methods of managing abdominal aortic aneurysm operation that reduce the operative mortality rate to less than 2%, despite the presence of coronary artery disease in nearly one half of the cases. They accomplished this by simply monitoring and managing cardiac function in patients with stable coronary artery disease and coronary bypass before or at operation for abdominal aortic aneurysms in patients with unstable coronary artery disease. I am sure that all of us would agree with this approach and I would like to add that the long-term (10-year) survival rate for patients with both coronary artery disease and abdominal aortic aneurysms who have had both coronary artery bypass and aneurysm replacement is as good as that in the patient without coronary artery disease who had aneurysm replacement.

DR. WAYNE JOHNSTON (Toronto, Ontario, Canada): The results of this study can be generalized to other groups of surgical patients. Clearly patients having aortic aneurysm repair have a very high incidence of coronary artery disease, but I suspect that many other populations of surgical patients who have an average age of 70 years have a similar high incidence.

The data from the Canadian Aneurysm Study supports the authors' conclusion, that patients without clinical or EKG evidence of coronary artery disease do not require further investigation for aneurysm repair.

This conclusion has very important practical and cost implications and is relevant to at least one half of the patients having aneurysm repair.

In the Canadian Aneurysm Study, 666 patients had elective or urgent operations by 72 surgeons during a 9-month period in 1986.

In this national study the overall mortality rate was 4.8% as compared to the authors' remarkable low mortality rate of 1.6% in their own series.

In this slide in yellow, 300 of the 666 patients in this study did not have clinical or EKG evidence of coronary disease, and their 30-day mortality rate was 0.8%. This mortality rate will not be reduced significantly by expensive cardiac investigation. For these patients without coronary artery disease, is invasive monitoring indeed necessary and will it improve the results?

In contrast, in the second group of patients, 366 of the 666 patients had clinical or EKG evidence of coronary disease and their mortality rate was 6.8%. These patients do warrant further investigation and coronary artery repair and/or appropriate medical and anesthetic management.

For these patients with coronary disease, what is, in fact, the most cost effective test? I did not reach a conclusion on this from reading the manuscript.

What is the sensitivity and specificity of dypyridmol thallium scanning for this group of patients? We have become disenchanted with this approach.

Do your results of ambulatory Holter monitoring, which you describe in the manuscript, improve screening in this group of patients in critical condition?

DR. CALVIN ERNST (Detroit, Michigan): This 16-year experience summarizes contemporary management of infrarenal abdominal aortic aneurysm repairs, which is difficult to duplicate. It is gratifying to know that the cardiac mortality rate is so low in asymptomatic patients with normal EKGs that we can justify minimal cardiac evaluation before operation.

Precise monitoring of left ventricular performance with preoperative fluid challenge has contributed substantially to these excellent early results. Insofar as critical care beds are available, at the Henry Ford Hospital we try to follow a similar protocol, but unavailability of ICU beds often precludes such studies. Nonetheless, among 991 patients who we have managed during the same time interval as reported by the authors, our fatal postoperative myocardial infarction rate was 2.7%. Like the authors of this study, we have had difficulty in precisely identifying those few individuals who would have benefitted from extensive preoperative cardiac evaluation. Therefore can you identify any markers, in retrospect, from the five group II patients who died and the seven who had nonfatal myocardial infarctions, whereby we can establish the cost effectiveness of extensive preoperative cardiac evaluation, including arteriography?

I would like to follow up on one of the questions that Dr. Crawford asked that relates to the classic report from the Henry Ford Hospital presented to this Association in 1966 by Szilagyi and Smith that life expectancy is doubled by repairing asymptomatic abdominal aortic aneurysms. Are the authors willing to speculate on whether this doubled life expectancy can be extended by prudent cardiac evaluation and myocardial revascularization before abdominal aortic aneurysm repair?

DR. GEORGE JOHNSON (Chapel Hill, North Carolina): I will try to emphasize some of the points already made. This is a prospective trial with 500 patients managed during a 16-year period, certainly a most difficult accomplishment that many of us could not do. The message is that there is a large group of patients with an abdominal aortic aneurysm and stable angina who have a sixfold times greater risk of dying of a postoperative cardiac problem.

In an attempt to predict which patients needed an Intensive Care Unit bed, Nolan and Meyer of our institution, the University of North Carolina at Chapel Hill, reviewed 474 patients operated on for peripheral vascular disease. Using Golman's criteria, in which class I is 0 to 5 points and class II is 6 to 12 points, we also were unable to predict the perioperative cardiac problems. This supports the conclusion of the presentation that we need better means of preoperative appraisal.

Although in 1975 we reported 100 elective aneurysms without a postoperative death, we have been unable to sustain these results. The enviable results reported by this group support their method of preoperative fluid homeostasis. The rest of us wish we had the Intensive Care Unit facilities to do likewise.

How many patients from group II crossed over to group III on the basis of the coronary angiogram and vice versa?

Of the various tests you used, which was the best predictor of postoperative cardiac problems?

The logical question is and has been put forth: do you now believe that a coronary angiogram should be performed on all of these patients? If not, were there any criteria for doing angiography based on the noninvasive tests?

This is another world class paper from the Brigham. I would like to emphasize that the thoughts expressed in this paper should be applied to all patients undergoing major operation. It emphasizes the point of Dr. Mannick's Presidential Address that basic surgical principles are important to all surgeons.

DR. NORMAN R. HERTZER (Cleveland, Ohio): As already indicated, these results are a tribute to a world class medical center, but they don't necessarily reflect cardiac risk elsewhere. During the 16 years that it took to collect the series of 470 patients reported, something on the order of one million other patients had their aneurysms resected at countless hospitals located in virtually every city across the United States. Their risk will never be known, but I can tell you this, it wasn't 1.7%.

A few years ago, data from the Cleveland Vascular Registry indicated that the early mortality rate for elective aneurysm resection was 6.5% in Northeastern Ohio. This figure still may be a conservative estimate of the risk of aneurysm resection throughout the country, and it doesn't even address the critical group of patients who have certified multiple-vessel coronary disease.

They have another problem, too. As Dr. Crawford indicated, they don't seem to live as long, even after successful operations.

During our initial experience with preoperative coronary angiography, 236 patients survived elective aneurysm resection at the Cleveland Clinic. In the presence of only mild to moderate coronary involvement, the 5-year life table survival rate was 79% and the cumulative cardiac mortality rate was only 6%. Patients who had advanced but compensated coronary lesions that did not yet warrant bypass procedures fared worse (71% and 11%, respectively), but the important distinctions occurred in those subsets of patients who were documented to have severe coronary disease. If bypass was performed in this specific setting, the 5-year survival rate was 75% and the cardiac mortality rate was 5%; if it was not, the 5-year survival rate was only 29% and the cardiac mortality rate was 34%.

One of the objectives of preoperative cardiac assessment (at least if we intend to influence late survival) is to identify these last two subsets, but because cardiac intervention occurred in only 6% of the patients in your series, I'm not sure that you have done that. Your early results are superlative, but I do have two questions.

Do you intervene with coronary bypass or PTCA more frequently now than you did 5 years ago? Finally, related to other remarks this morning, do you have any preliminary information concerning late survival rates in your group II patients?

DR. RALPH DEPALMA (Washington, D.C.): Some time ago we published the results for cardiac monitoring during aortic surgery and we noticed that in asymptomatic patients, those without coronary disease, that nitroprusside unloading or unloading in infrarenal cross-clamping may have been deleterious.

I noticed in the presentation that it was mentioned that all cases had afterload reduction with aortic clamping.

How many cases were infrarenal cross-clamps and how many were suprarenal cross-clamps?

Do you really always do afterload reduction on clamping the infrarenal aorta?

DR. RONALD J. STONEY (San Francisco, California): I think a hidden message that I take away from this is that, of the 500 patients who were submitted to operation, the only patients who died were patients who died of myocardial infarction or pulmonary embolus, so there are no deaths due to any technical problems. As vascular surgeons, every once in a while we experience postoperative hemorrhage, multi-organ failure, or sepsis. Rarely are these complications fatal. This is a truly remarkable series. There are none of the usual causes of perioperative morbidity that may result in a mortality.

DR. JAMES C. STANLEY (Ann Arbor, Michigan): Many cardiologists, including a recent president of the American College of Cardiology, have suggested that the exercise ECG is the best means to assess the presence or absence of silent coronary artery disease. This is distressing to one such as myself, coming from a medical center involved in the initial assessments of dipyridamole-thallium studies for occult coronary artery disease.

At the University of Michigan, all patients undergoing aortic reconstructive surgery, except those who have had recent coronary artery bypasses and have been evaluated following such, undergo preoperative dipyridamole-thallium studies to access the functional adequacy of their coronary circulation. Approximately 10% of our patients have what has been considered to be significant redistributions of myocardial blood flow, and nearly 75% of those have undergone either balloon angioplasty or coronary artery bypass before the aortic operation is performed. In some respects these individuals are similar to group III patients in the Brigham experience. One particular issue deserves note regarding dipyridamole-thallium studies. Interpretation of this particular test should not be categorized as simply positive or negative. A minor area of redistribution cannot be equated with a large area of redistribution in the region of the left anterior descending coronary artery. Similarly, in patients with long-standing hypertension and left ventricular hypertrophy, this particular means of testing may not have the sensitivity necessary to be useful in defining the presence or absence of occult coronary artery disease.

On an historical basis, our overall cardiac morbidity accompanying aortic surgery has been markedly reduced using a strategy of preoperative dipyridamole-thallium testing. However, as in many other situations, this has been a nonrandomized experience and the fate of these patients, had they not undergone a coronary artery intervention, remains undetermined. One might suspect that a certain number of them would have done quite well in the short run. Although the long-term benefit afforded by such aggressive diagnostic and therapeutic approaches to silent coronary artery disease may be considered great, such has yet to be proved. One must also be aware that this is an expensive form of screening, and the total health care cost of managing patients with silent coronary artery disease by this manner may be prohibitive.

There were a reasonable number of coronary events in the group II Brigham patients, nearly 4.5%. One might have speculated that some form of myocardial flow testing such as an exercise-thallium, dipyridamole-thallium, or adenosine-thallium studies, would have unmasked these patients. Perhaps Dr. Whittemore could define what one test they currently believe has the greatest specificity for evaluating these patients, realizing the heterogeneic manner in which these studies may have been obtained in their own patient population. In as much as major vascular surgery has become better standardized in regard to both the operative techniques and anesthetic management, it would seem prudent to better define those patients in the group II category, who might be at risk for myocardial ischemia during an otherwise uneventful operation.

DR. LOUIS DEL GUERCIO (Valhalla, New York): I would like to ask Dr. Golden in what proportion of the group I patients did the preoperative Swan-Gans catheter data significantly alter the fluid management or inatropic therapy?

DR. D. SHAH (Albany, New York): I have one question. Are these patients all comers, or were any patients turned down, and, if so, what were the criteria for turning down a patient with aneurysm?

DR. JOSEPH M. CIVETTA (Miami, Florida): Initial efforts in these patients were directed at preoperative identification, hoping that preoperative evaluation and augmentation of hemodynamic function would be sufficient to minimize the postoperative cardiac-related mortality rate. Given safer coronary bypass and angioplasty procedures, I think the most important aspect of this paper is identifying the need for a more aggressive approach to correct coronary artery disease before operation, not just optimizing cardiac function.

DR. ANTHONY D. WHITTEMORE (Closing discussion): I will try to take all questions, one at a time, and see if we can answer them before sundown.

Dr. Crawford, although I don't take any solace from your raising the spectors of our next two patients, I am reminded of the privilege we had 10 years ago of presenting our initial aneurysm experience of 110 patients before this Association with no operative deaths within 30 days. Shortly thereafter, two of our patients sustained fatal pulmonary emboli, so I look forward to the next 2 weeks with fear and trepidation, and I hope that your predictions do not become reality.

Should we liberalize the use of coronary arteriography and coronary bypass in our group II patients? We don't see that as a trend in the future. We are finding fewer patients who benefit from this approach. Dr. Hertzer has shown the routine use of coronary angiography and coronary bypass resulted in a 5.6% mortality rate, a finding that modified his perspective on these patients. The 2.4% mortality rate in our group II patients seems more favorable.

With respect to the life-expectancy data, our initial series in 1980 and the update in 1985 demonstrated a 75% to 80% 5-year survival rate, which is insignificantly different from that expected from the normal population. Whether that holds true with this current group is unknown. These data are being accumulated, and it may well be that patients in group II have a reduced life expectancy compared to those in group I. As Dr. Ernst suggested by his comment, the life expectancy may be significantly improved for those patients having initial coronary bypass.

Should we decide to go ahead with preliminary coronary bypass in the group III patients, the majority of such aneurysms are repaired within the month. We haven't hesitated to minimize the time interval during which they may rupture.

Dr. Johnston's question pertains to the necessity for invasive monitoring in group I patients, and I think that is a very important consideration, as is reflected by several other questions. Preoperative invasive monitoring is probably not necessary for these group I patients, and with the cost-containment guidelines we are all operating under, as well as space constraints in our ICUs, this is a particularly pertinent issue. While it may well prove that we do not have to admit these patients to the ICU the night before, we do feel strongly that all patients will have to be volume loaded one way or another in an effort to manage declamping most effectively.

Three of the discussants, Dr. Johnston, Dr. Ernst, and Dr. George Johnson, asked us about the most cost-effective predictive screening test with respect to our patients in group II. We were unable to arrive at any single common denominator that was truly predictive and no single test proved infallible. The only light I can shed on this pertains to our ambulatory Holter monitoring data, which may prove the most sensitive of all. In a group of nearly 200 patients in our institution who underwent vascular surgery, some of whom underwent aneurysm repair, the sensitivity and the specificity of ambulatory Holter monitoring for a 24-hour period before operation exceeded 90% in predicting postoperative cardiac events. It appears that ambulatory silent ischemia is perhaps one of the most sensitive predictors. It will certainly be to our advantage if this proves to be the case because it is most cost effective.

Dr. George Johnson asked whether we had any substantial cross-over between groups II and III, and the answer is no. Of course, it is difficult for us to look at this entirely prospectively because many times the cardiologists made the initial decisions as to the necessity for coronary arteriography or other tests. Again no particular test proved to be an infallible predictor.

Dr. Johnson also asked us whether we would consider routine coronary arteriography for our patients in group II. Once again, referring back to

Dr. Hertzer's data, this appears to be unnecessary in that our selective management has produced a very low 2.4% mortality rate in that group.

Dr. Hertzer asked if we intervene more often in group II patients with coronary angiography and coronary bypass. The answer is not really. In the series of 227 patients we reported 5 years ago, there were 12 such individuals who were managed in this fashion and only 28 individuals in our current series of 500, so there has not been a significant increase in our intervention.

Dr. DePalma has referred to the potential myocardial depression associated with nitroprusside, and we have used nitroglycerine in such circumstances as well. All of the aneurysms in this series were infrarenal in location.

Dr. Stanley brought up the spector of silent ischemia, and I think it is a very important consideration. We need to separate the physiologically failing ventricle from the intact ventricle that is merely susceptible to ischemia. These represent two related, but very different problems, and need to be managed accordingly. The ambulatory ischemic Holter monitor may do just that by allowing us to identify the myocardium that is truly susceptible to ischemia. We, too, have had difficulty interpreting dipyridamole-thallium redistribution and your point is well taken.

Dr. Del Guercio also asked us about the necessity for routine Swan-Ganz catheters for fluid management in group I patients. We continue to believe that this is important. It may not be necessary to admit these patients formally to an ICU the night before to monitor that volume infusion, but certainly during operation and for the first 24 to 36 hours after operation, we found that invasive monitoring provides invaluable assistance in managing the fluid requirements and insuring that group I patients remain at low risk for death.

Finally, Dr. Shah asked whether we have turned down any of our patients for aneurysm repair. Any patient who has come to us with an aneurysm exceeding 5 cm in diameter has had that aneurysm repaired, with extraordinarily few exceptions. Age, in and of itself, has not been a contraindication, and even those patients with severe reduction in FEV-1 and/or ejection fraction can safely undergo aneurysm repair with appropriate invasive monitoring.

Effects of Recombinant Human Growth Hormone on Donor-site Healing in Severely Burned Children

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The beneficial effects of growth hormone on wound healing in severely burned children were studied. Forty patients who were 2 to 18 years old, with 40% or more total body surface area (TBSA) and 20% or more TBSA full-thickness flame or scald burns, were randomized in a double-blind study to receive placebo or 0.1 mg/kg/day recombinant human growth hormone (rHGH) until the first donor site healed or to receive 0.2 mg/kg/day rHGH or placebo from admission throughout hospitalization. Patients receiving 0.2 mg/kg/day rHGH demonstrated significantly higher serum IGF-1 levels at 4.8 ± 1.7 U/mL compared to placebos at 1.6 ± 0.4 U/mL ($p < 0.05$) and a significant decrease in donor-site healing times compared to placebo ($p < 0.05$). Length of hospital stay (LOS/%TBSA) was decreased from 0.80 ± 0.10 days/%TBSA burned in the placebo group to 0.54 ± 0.04 days/%TBSA burned in the 0.2 mg/kg/day treatment group ($p < 0.05$). This translates, for the average 60% TBSA burned patient, to a decrease in LOS from 46 to 32 days.

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HYPERMETABOLISM, CHARACTERIZED BY increased glucose flow, severe protein and fat wasting, increased oxygen consumption, and a negative nitrogen balance, is typical of the human response to injury and infection.[1,2] In no other disease state is this so pronounced as after a thermal injury.[3] Evidence indicates that as the catabolic state continues, weight loss, lean muscle mass loss, immunologic compromise, poor or delayed wound healing, and prolonged recovery times may result.[4–7] In severely burned children, this response is often manifested by a temporary or sustained decrease in physical growth and development.[8]

The purpose of this study was to test the hypothesis that the administration of recombinant human growth hormone (rHGH) to severely burned children would attenuate the morbid catabolic response following burn injury and increase the rate of wound healing.

Methods

Study Design

Patients selected for this study were between 2 and 18 years old, of either sex, with more than 40% total body surface area (TBSA) burn and 20% TBSA full-thickness flame or scald burns that required skin grafting with donor sites harvested from the upper thigh, buttock, arm, or scalp. Patients with previous grafting procedures performed at the referring institution and those with multiple fractures or associated injuries to the head, chest, or abdomen that required additional specific therapy were excluded from the study.

In a two-phase, double-blind protocol, subjects were assigned to 0.1 mg/kg/day rHGH, 0.2 mg/kg/day rHGH, or placebo by the provider of rHGH (Genentech Inc, San Francisco, CA) using a random numbers chart balanced for age, cause, and extent of burn injury. Drug vials were blinded and numbered by Genentech Inc. and mailed to the investigator in indistinguishable packages. In the first phase of the study, 24 patients were randomized to receive placebo (normal saline) or 0.1 mg/kg/day rHGH from the first autograft until donor-site healing. In the second phase, the subsequent 16 patients received 0.2 mg/kg/day rHGH or placebo from admission through hospital stay. Placebo and rHGH were administered subcutaneously in the 0.1 mg/kg/day dosage group and intramuscularly in the 0.2 mg/kg/day group each morning at approximately

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the same time. Baseline and weekly laboratory studies included complete blood counts with differential, urinalysis, serum chemistry panels, and liver function tests that were analyzed by independent laboratories to ensure that the double-blind protocol was maintained (SmithKline Beecham Clinical Laboratories, Van Nuys, CA) and serum IGF-1, rHGH, and rHGH antibody levels were performed using radioimmunoassay (Genentech Inc, San Francisco, CA). All blood samples for baseline determinations were drawn before the first rHGH dose. Clinically indicated laboratory studies were completed according to standard in-house protocols.

All subjects received resuscitation fluids to meet calculated requirements based on 5000 mL/m^2 BSA burn/day plus 2000 mL/m^2 BSA/day of lactated Ringer's solution during the first 24 hours and 3750 mL/m^2 BSA burn/day plus 1500 mL/m^2 BSA/day of 5% dextrose with 0.3% normal saline thereafter. Enteral nutrition, either oral or through feeding tubes, was provided to meet calculated caloric requirements of 1800 kcal/m^2 BSA/day plus 2200 kcal/m^2 BSA burn/day and recalculated as the wound healed. Exogenous albumin was administered intravenously to maintain serum albumin levels between 2.5 and 3.5 g/dL. Calorie yielding supplements, including intravenous albumin and dextrose solutions, were included in the final caloric intake determinations.

Wound Care

All subjects were treated by early excision and grafting with the entire burn wound excised, except the face and perineum, within 48 hours of admission. Wounds were covered with 2:1 meshed autograft, 4:1 meshed autograft with 2:1 meshed cadaveric allograft overlay, or 2:1 meshed allograft, if sufficient donor sites were unavailable to provide complete 4:1 autograft coverage. When donor sites were healed, patients were returned to the operating room for closure of remaining open areas and to replace areas where homograft alone was used as a temporary cover. Scarlet red impregnated fine mesh gauze (Sherwood Medical, St Louis, MO) was applied to all study donor sites and the patient positioned so that the donor site was exposed to air. If donor sites failed to dry or developed excess fluid accumulation, a 40-watt heat lamp was positioned 18″ from the donor site and heat applied for 20 minutes each hour. In addition 0.25% sodium hypochloride/0.3% sodium phosphate solution soaks were applied for 20 minutes each hour until donor sites dried.

Healing Time of Donor Site

On the third postoperative day, a trained evaluator examined, measured, and photographed the donor site using a standard camera and focal distance. Using a sterile technique, each of the four corners of the gauze was gently lifted using sterile forceps and minimal tension to determine if the dressing adhered to the underlying tissue. The unattached dressing was trimmed away and the site rephotographed. This examination procedure was performed on alternate days until the wound healed, as indicated by complete removal of the dressing.

rHGH Profiles

A temporal profile of rHGH was determined by measuring growth hormone concentrations during a 24-hour period. Nutrition was given at a constant rate *via* enteral feeding tubes during the study period. Six patients receiving 0.1 mg/kg rHGH and five receiving 0.2 mg/kg had serial blood samples obtained 0, 0.5, 1, 2, 3, 4, 5, 6, 9, 12, and 24 hours after the 0800-hour administration of rHGH for the purposes of determining the pattern of rHGH uptake and disappearance. Growth hormone levels were measured by an independent laboratory using radioimmunoassay techniques (SmithKline Beecham Clinical Laboratories, Van Nuys, CA).

Statistical Analysis

All information in the text and tables is expressed as means ± SEM. Differences between the means were tested using t tests. When group variances were unequal, the Cochran-Cox two-tailed t test was used to detect differences. Regression techniques were used to determine the association between length of stay and percentage of third-degree burn and to estimate the effect of age on healing times.

This study was reviewed and approved by the Institutional Review Board (IRB) of the University of Texas Medical Branch (OSP 88-56), constituted according to state and federal guidelines. Informed consent/assent was obtained from the patient's parents/guardians and the patient as well if he or she was older than 7 years.

Results

In 12 patients receiving 0.1 mg/kg/day of rHGH and 12 receiving placebo from the day of the first autografting procedure until donor site healing, no differences in the rate of the first donor-site healing, IGF-1 levels, or adverse events associated with the 0.1 mg/kg/day dosage were observed. In a clearance study comparing two dosages of rHGH in six patients treated with 0.1 mg/kg/day and five treated with 0.2 mg/kg/day (Fig. 1), no difference could be shown in the basal levels of rHGH between the two groups at 0.7 ± 0.1 compared to 1.2 ± 0.2 ng/mL, respectively. Peak levels of rHGH were 42.5 ± 1.8 ng/mL for the 0.1 mg/kg/day group compared to 70.8 ± 15.3 ng/mL for the 0.2 mg/kg/day group ($p < 0.05$). Serum concentrations of the drug were significantly higher 12 hours after administration of the 0.2 mg/kg/day dosage com-

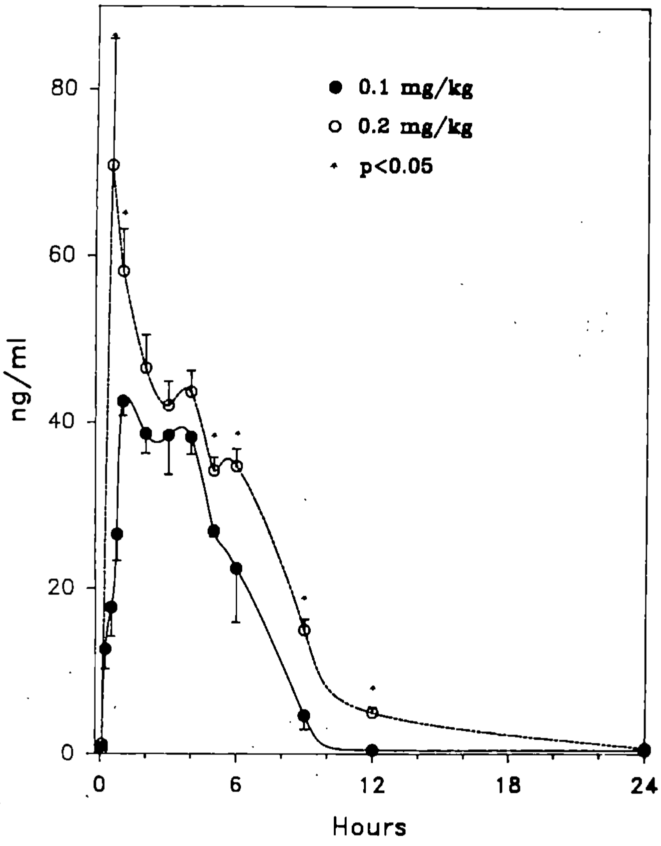

FIG. 1. Recombinant human growth hormone disappearance curves of a single injection of 0.1 and 0.2 mg/kg/day are shown.

pared to the 0.1 mg/kg/day dosage (Fig. 1). With these data the IRB granted that the study be redirected, and the subsequent 16 patients were randomized to receive 0.2 mg/kg/day or placebo from the time of admission throughout hospitalization.

No demographic differences between the placebo groups of the 0.1 mg/kg/day group and those of the 0.2 mg/kg/day group could be distinguished, and thus data from placebo patients were pooled. There were no significant differences in age, TBSA (%) or TBSA full-thickness burn, or postburn day of admission among the three designated groups (Table 1).

During the first few days after burn, the subjects received most of their calories in the form of enteral milk or soybean-based milk substitute for lactose-intolerant patients (0.66 kcal/mL) orally or through small intestine feeding tubes. As clinical status improved and appetite returned, milk was administered to supplement voluntary consumption of a menu-selected diet to achieve an actual caloric intake of 1800 kcal/m^2 BSA/day plus (939 ± 107) kcal/m^2 BSA burn/day. No patient received total parenteral nutrition. No significant differences in the calories received between the groups or in the ratio of substrate nutrients received could be shown (Table 2). Exogenous intravenous albumin was administered at a rate of 78 ± 18 g per patient during the hospital stay to maintain serum albumin levels at 2.8 ± 0.1 mg/dL.

Table 3 shows that no significant elevations could be demonstrated in serum liver function tests, blood urea nitrogen, or glucose levels although, as in all burn patients, glucose levels were elevated approximately 33% above normal. Table 4 shows that the first and second donor site healing times and LOS/% TBSA burn were significantly decreased in the 0.2 mg/kg/day group relative to controls, with hospital stay decreased from 0.8 ± 0.1 to 0.54 ± 0.05 days/% TBSA burn ($p < 0.05$), representing an overall decrease in length of stay from 46 to 32 days for the average of 60% TBSA burn. Figure 2 demonstrates that LOS was decreased when calculated on the basis of the percentage TBSA burned from 0.65 days/% TBSA burn for the controls to 0.59 days/% TBSA burn in the 0.2 mg/kg/day group. By regression analysis no significant effect of age on healing times could be demonstrated. Four patients in the 0.1 mg/kg/day rHGH group and two patients in the 0.2 mg/kg/day rHGH group had sufficiently elevated serum glucose levels to necessitate exogenous insulin to maintain glucose levels at less than 250 mg/dL, although no control patients required insulin supplementation. These six hyperglycemic rHGH-treated patients required 48 ± 16 μ per day exogenous insulin for a period of 10 ± 3 days to maintain acceptable serum glucose levels. However, when patients who received insulin supplementation were excluded from the analysis, donor-site healing times and LOS/% TBSA burn remained significantly shorter in the 0.2 mg/kg/day treated group (Table 5). When LOS in days for the 0.2 mg/kg/day patients not receiving insulin supplementation was compared to pla-

TABLE 1. *Characteristics for Severely Burned Children Between 2 and 18 Years of Age Assigned to a Double-blind Study to Receive rHGH or Placebo*

Group	n	BSA (m^2)	Age (years)	TBSA Burn (%)	TBSA Full Thickness (%)	PBD Admitted
Placebo	18	1.2 ± 0.1	10.2 ± 1.2	60 ± 3	43 ± 5	3.1 ± 1.6
0.1 mg/kg/day	12	1.0 ± 0.1	7.5 ± 1.3	58 ± 5	47 ± 6	2.4 ± 0.9
0.2 mg/kg/day	10	1.0 ± 0.1	7.0 ± 1.3	57 ± 5	41 ± 7	3.5 ± 2.5

Data presented as mean ± SEM.

BSA, body surface area; TBSA, total body surface area; PBD, postburn day; rHGH, recombinant hormone growth factor.

TABLE 2. *Caloric Intake During Hospital Stay*

Group	n	Calculated Kcal/m^2/d Required	Mean Daily Substrate Intake				
			IV Albumin (kcal/m^2 BSA)	Protein (kcal/m^2 BSA)	Carbohydrate (kcal/m^2 BSA)	Fat (kcal/m^2 BSA)	IV (kcal/m^2 BSA)
Placebo	18	2906 ± 114	6.6 ± 1.6	545 ± 52	1007 ± 60	1093 ± 91	174 ± 37
0.2 mg/kg/day	10	2887 ± 170	5.6 ± 2.9	578 ± 38	1161 ± 53	1228 ± 75	144 ± 38

Data presented as Mean ± SEM.

IV, intravenous.

TABLE 3. *Liver Function, Serum Glucose, and BUN*

Test	Day 0 (n)	Day 7 (n)	Day 14 (n)	Day 28 (n)
SGOT				
Placebo	98 ± 38 (18)	45 ± 4 (16)	83 ± 38 (10)	30 ± 4 (3)
0.2 mg/kg/day	50 ± 12 (10)	30 ± 3 (10)	23 ± 3 (5)	26 ± 2 (3)
Normal range	5–40 u/L			
Alkaline Phosphatase				
Placebo	73 ± 27 (18)	151 ± 15 (16)	130 ± 15 (10)	148 ± 14 (3)
0.2 mg/kg/day	82 ± 14 (10)	135 ± 20 (10)	111 ± 24 (5)	129 ± 22 (3)
Normal range	35–140 u/L			
Glucose				
Placebo	151 ± 13 (18)	141 ± 13 (16)	114 ± 6 (10)	125 ± 12 (3)
0.2 mg/kg/day	104 ± 13 (10)	112 ± 9 (10)	140 ± 19 (5)	138 ± 28 (3)
Normal range	60–100 mg/dL			
BUN				
Placebo	14 ± 2 (18)	18 ± 9 (16)	12 ± 2 (10)	13 ± 3 (3)
0.2 mg/kg/day	13 ± 2 (10)	14 ± 2 (10)	12 ± 1 (5)	15 ± 2 (3)
Normal range	8–21 mg/dL			

Means ± SEM; normal ranges provided by SmithKline Beecham Clinical Laboratories.

n, sample size.

BUN, blood urea nitrogen; SGOT, serum glutamic oxaloacetic transminase.

cebo (26 ± 12 days *versus* 46 ± 25 days, respectively), a significant difference at $p < 0.05$ was shown.

No treated subjects exhibited growth hormone antibody formation during rHGH treatment. With the administration of 0.2 mg/kg/day rHGH, IGF-1 levels increased three times compared to controls (4.8 ± 1.7 [n = 10] *versus* 1.6 ± 0.4 [n = 17], respectively, $p < 0.05$). The rate of donor-site healing with each harvest decreased approximately 2 to 4 days in the 0.2 mg/kg/day rHGH treatment group (Table 4), with a net decrease in length of hospital stay from 0.8 ± 0.1 days/% TBSA burn to 0.54 ± 0.05 days/% TBSA burn, or approximately a 14-day decrease in hospital stay for the average 60% TBSA burn. There were no deaths in any group or differences in the number of septic episodes among the groups.

Discussion

The overall effect of growth hormone on protein metabolism has been well illustrated by documented increases in linear growth, improvement of nitrogen balance, increase in IGF-1 levels, and increasing body cell mass after the administration of rHGH to growth hormone-deficient children.[9] Attempts to modify the postburn hypermetabolic response have been made using propranolol,[10] supernormal doses of insulin and potassium[11] and growth hormone. Our studies of the metabolic effects of beta adrenergic blockade in major burns have been shown to be of benefit in decreasing myocardial work and oxygen consumption but deleterious regarding increased protein breakdown.[10] The administration of supernormal doses

TABLE 4. *Donor Site Healing Times and Length of Hospital Stay in Studied Patients*

Group	Donor Site Healing Times (days)			LOS/%TBSAB	IGF-1 (U/mL)
	1st Harvest	2nd Harvest	3rd Harvest		
Placebo	9.1 ± 0.4 (17)	9.0 ± 0.7 (4)	8.3 ± 1.3 (4)	0.80 ± 0.09 (18)	1.6 ± 0.4 (17)
0.2 mg/kg/day	7.4* ± 0.5 (10)	6.0* ± 0.4 (4)	6.5 ± 0.6 (4)	0.54* ± 0.04 (10)	4.8* ± 1.7 (10)

Data presented as Means ± SEM, *t test, significance accepted at $p < 0.05$, when compared to placebo.

LOS, length of hospital stay; TBSAB, total body surface area burn.

TABLE 5. *Donor Site Healing Times and Length of Hospital Stay (LOS) in Patients Not Receiving Insulin Supplementation*

Group	Donor Site Healing Times (days)				
	1st Harvest	2nd Harvest	3rd Harvest	LOS/%TBSAB	IGF-1 (U/mL)
Placebo	9.1 ± 0.4 (17)	9.0 ± 0.7 (4)	8.3 ± 1.9 (3)	0.79 ± 0.10 (17)	1.6 ± 0.4 (17)
0.2 mg/kg/day	7.4* ± 0.6 (8)	5.7* ± 0.3 (3)	6.3 ± 0.9 (3)	0.50* ± 0.05 (8)	5.3* ± 2.1 (8)

Data presented as Means ± SEM, * Two sided t test, significance accepted at $p < 0.05$, when compared to placebo.

TBSAB, total body surface area burn.

of insulin and potassium have been used in an attempt to increase anabolic activity.[11] However this technique has not become clinically accepted except to treat gross hyperglycemia. In our study, six of the rHGH-treated patients required 43 ± 16 μ/day of insulin for 10 ± 3 days; however fewer of the 0.2 mg/kg/day group required supplementation and changes effected by administration of rHGH in IGF-1 levels, hospital stay and donor site healing times were no different when those patients treated with exogenous insulin were excluded. We do not think that insulin administration accounts for the anabolic effects observed in this study.

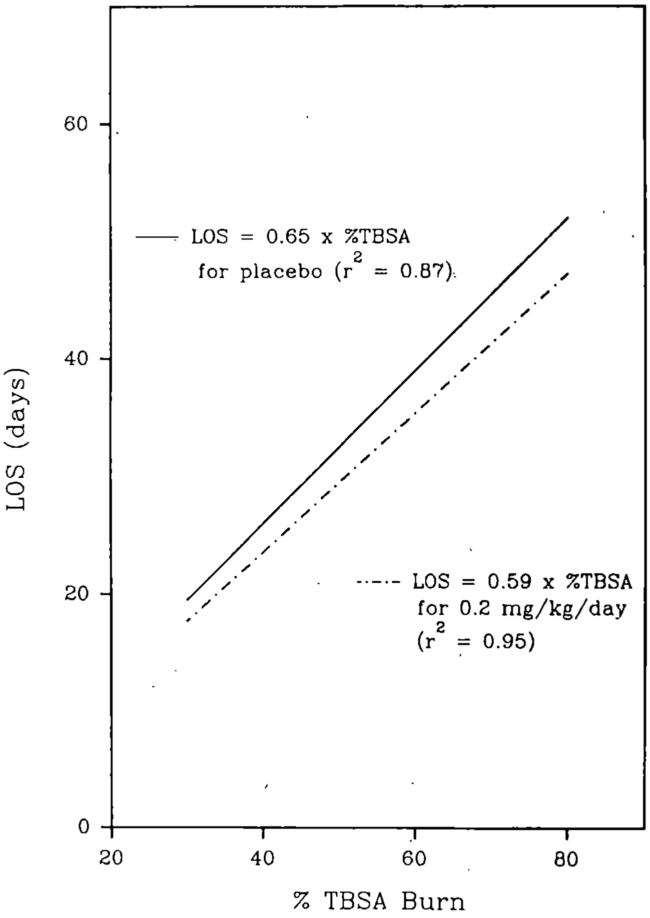

FIG. 2. A simple linear regression was used to study the relationship between length of hospital stay and percentage of area identified as burn. *Significant difference between slopes at $p < 0.05$.

Growth hormone, as a pituitary extract, has been shown to improve nitrogen balance and decrease weight loss in hypermetabolic patients following thermal injury.[2,3] Gump et al.[12] demonstrated that burned rats receiving adequate nutrition and growth hormone did not suffer a catabolic response, while Soroff et al.[13] demonstrated similar positive effects of human growth hormone administration in patients during the anabolic phase of burn recovery. Liljedahl et al.[14] and Wilmore et al.[15] showed that growth hormone caused a significant improvement in nitrogen and potassium balance in the postburn period with no significant side effects. It was the clinical impression of those investigators that the nitrogen retention, as related to growth hormone administration, was accompanied by accelerated wound healing and apparent decreases in morbidity rate and hospitalization time. Lack of widespread availability of the pituitary extract tempered clinical investigations until rHGH became available.

The recent availability of rHGH has enabled a number of recent studies that have demonstrated that growth hormone promotes nitrogen retention and protein synthesis in patients receiving hypocaloric parenteral nutrition[16,17] and enhances the re-epithelialization of split-thickness skin graft donor sites in adult patients.[18] In addition growth hormone has been noted to increase circulating IGF-1 levels, cell mass, and linear growth in growth hormone-deficient children.[9] The anabolic effects of rHGH are thought to be mediated by IGF-1 because growth hormone treatment has been shown to increase their circulating levels.[19] The role of IGF-1 as a second messenger for growth hormone was proposed by Salmon et al.,[20] who showed that cartilaginous growth was stimulated by a factor derived from the serum of animals treated with growth hormone. Subsequent studies have confirmed that IGF-1 production is growth hormone dependent and suggest that the liver is a major site of IGF-1 production,[21] in addition to production at multiple sites, and that specific organ levels of IGF-1 are variable.[22,23]

This study was originally designed with one half of the patients receiving 0.1 mg/kg/day growth hormone and the other half receiving placebo until the first donor site healed. Preliminary data indicated that there was no difference in the rate of donor-site healing or IGF-1 levels between the two groups and that no harmful effects were noted. Because IGF-1 is believed to mediate the effects of growth hormone, the study was redirected to evaluate a group of patients using 0.2 mg/kg/day throughout hospital stay to determine if a higher dose of growth hormone given during a longer period would result in an increase in IGF-1.

The pharmacokinetic curves of rHGH disappearance in this study document basal serum concentration levels of growth hormone in burned children to be lower than those reported for normal children at 1 ± 0.2 *versus* 5 to 40 ng/mL (SmithKline Beecham Clinical Laboratories), respectively. In addition the peak rHGH concentration occurs earlier in burned than in growth hormone-deficient children and the serum profile indicates a more rapid disappearance of growth hormone in the burned patients.[24] This pharmacokinetic data suggests that twice-daily (BID) administration of rHGH would maintain sustained levels of growth hormone. In this study we administered rHGH only in the morning and because the diurnal release of growth hormone in normal children is greater at night, consideration of rHGH administration at that time or in a BID regimen may be appropriate.

This study has demonstrated, using a once-a-day administration, a 2-to-4-day decrease in the rate of each donor site healing with administration of 0.2 mg/kg/day rHGH ($p < 0.05$), with a net decrease in length of hospital stay of 0.8 ± 0.1 to 0.54 ± 0.05 days/% TBSA burn ($p < 0.05$), which represents a decrease of 14 days for burns averaging 60% TBSA, with a subsequent decrease in morbidity rate and hospitalization costs.

Long-term studies to determine effects on body composition and growth arrest with different doses are clearly indicated. Furthermore the association of the threefold increase in IGF-1 levels with these salutary results would warrant investigation of this now-available recombinant product as a more direct agent that may decrease catabolic effects, increase wound healing, and perhaps relieve the transient insulin resistance observed in some of the rHGH-treated patients.

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DISCUSSION

DR. DOUGLAS WILMORE (Boston, Massachusetts): We have been told during the past 10 years that we are living in the middle of a biologic revolution. We hear much about cell biology and how this will affect the care of our surgical patients.

About 20 years ago I spent a number of hours talking with Stein-Otto Liljedahl, the renowned Swedish surgeon known to many of the senior members of this Association. He shared with me his thoughts and dreams about how surgical patients would be cared for in the future; he speculated that growth hormone and other growth factors would be used to accelerate wound healing.

Harry Soroff here in the United States, working with Curtis Artz, also believed that growth hormone would affect the metabolic response of the surgical patients and injured patients and enhance their rates of wound healing. Harry Soroff should be recognized as one of the individuals in this country who spent a great deal of time and a great deal of work on initial studies using growth hormone.

In the early 1970s, Basil Pruitt, Dick Mason and I, working at the U.S. Army Institute of Surgical Research in San Antonio, had the opportunity to study the effects of pituitary-extracted growth hormone in burn patients. Remember, growth hormone was an exceedingly precious substance at this time. It could only be extracted from human pituitaries and hence there was very little of it available. We saw tremendous positive effects in this very small group of patients given growth hormone during a short period of time.

The dramatic breakthrough came in the early 1980s. Instead of having the world's amount of growth hormone in a single vial, recombinant bioengineering technique allowed the manufacture of growth hormone in large quantities. Not only could children who were growth hormone deficient be provided with this needed agent, but also physicians could explore its use in other areas.

We have performed five randomized, double-blind, placebo-controlled trials in the last 3 years using various agents in an attempt to accelerate surgical recovery and wound healing. When we finished our growth hormone trial in adult patients, we went to the primary care nurses and asked if they could identify the patients who received growth hormone. The selection by the burn care nurses was 96% accurate, and when you asked them why they identified the patients who received growth hormone, they said that they observed enhanced wound healing in these individuals compared to controls. Dr. Herndon's study has captured this dramatic effect. He has reduced length of study by about 14 days in a patient with a 60% burn. That is at least a saving of $14,000 to $25,000 and clearly provides the financial incentive necessary to pay for the drug and benefit to the patient.

There is a relationship between IGF-I generation and healing. If you examine your individual patient data, do the patients who have very high levels of IGF-I have the fastest rates of healing, and, do those patients who could not generate those high levels have much lower rates of healing?

We have seen changes in strength in patients receiving growth hormone. Did you look at strength and endurance? Could you see any other types of effects in rehabilitation?

In our hospital, we have an experience now approaching about 3000 patient days with growth hormone administration to surgical patients. Of those 3000 days, we have seen another possible complication and that has been hypercalcemia, which occurred in approximately 75 of the 3000 days. Have you experienced hypercalcemia in this younger group of patients who are growing? It may well be that our older patients who are in bed and are more prone to mobilize calcium may demonstrate this particular complication.

Have you considered topical use of growth hormone, or have you any experience with the use of IGF-I along?

This is the first in a series of stories that will be repeatedly told over the next 10 to 20 years; specific therapy will be developed to accelerate surgical recovery. I congratulate the authors on their diligent and careful scientific approach to this subject.

DR. BASIL A. PRUITT, JR. (Fort Sam Houston, Texas): I, too, rise to compliment the authors on their interesting study demonstrating a dose-related effect of exogenous recombinant human growth hormone on circulating levels of growth hormone.

This paper represents another in a series of papers by Dr. Herndon in which he has detailed the techniques of care that he uses in the treatment of severely burned children.

The treatment techniques described in those earlier papers have been associated with an impressive improvement in survival of extensively burned patients, and, in fact, may account for some of the differences observed in this study, independent of growth hormone.

Even though the authors have noted that there was no significant difference in calories received by the two groups of patients, that appears to refer to the per-day nutrient supply. Calculations using the data in Table 2 of their manuscript reveal a cumulative difference of more than 9000 Kcal over the 32 days representing the length of stay of the treatment group. The treatment group received 99,731 Kcal *versus* 90,419 Kcal for the controls.

Several years ago, as Dr. Wilmore mentioned, he conducted studies at our Institute demonstrating that growth hormone improved nitrogen balance only when nutrient supply met estimated needs.

In the treatment group in this study, total mean daily substrate intake was 3116.6 Kcal/m^2/day, clearly greater than the calculated requirement of 2887 Kcal/m^2/day.

It is troublesome, however, that the total mean daily substrate intake was less than the calculated requirement in the controls.

In light of that difference, how is the relative importance of growth hormone and variation in nutrient supply assessed?

Conversely, there may have been changes in other variables that could account for a type II error by depressing endogenous growth hormone production. Because hypothyroidism is known to decrease growth hormone messenger RNA, and, at least in rats, elevation of plasma-free fatty acid levels is known to suppress growth hormone releasing factor-induced growth hormone secretion by stimulating somatostatin, it would be interesting to know whether there were depressed circulating levels of thyroid hormones or elevated levels of free fatty acids or somatostatin in the treatment groups.

Studies in animal models have shown that growth hormone increases collagen formation in implanted cellulose sponges. Consequently I wonder whether such an effect was manifested by an increase in hypertrophic scar formation in any of the treated patients.

The data in Table 4 indicate that there was a reduction in healing time of 2 to 3 days, for each of three successive split-thickness skin graft harvests. Because that reduction in healing time appears to account for only about one half of the reduction in the length of hospital stay, what accounts for the other half of that reduction? Did the growth hormone accelerate healing of unexcised burn, or did it increase the take of skin grafts so that fewer grafting episodes were required?

Just this past month the authors, as they noted in the introduction, reported that children with burns of more than 40% of the body surface experience a significant growth delay, and I ask whether that growth delay was reduced in these patients treated with the growth hormone?

I enjoyed this paper that suggests that administration of exogenous growth hormone beneficially influences wound healing, even in critically injured patients.

DR. J. WESLEY ALEXANDER (Cincinnati, Ohio): This study shows two major benefits. The first is a decrease in hospital stay, which is really quite a striking reduction. One must realize that the reduction of hospital stay that Dr. Herndon has reported stands on top of what is already one of the best records for length of hospital stay in the United States. Most burn units are happy to have a hospital stay of 1 day per percentage of total body-surface area burned. Dr. Herndon's unusual hospital stay is better than that at about 8 days and with the treated patients, this is reduced to 0.53 days, which represents about a 50% reduction in hospital stay from what might be considered a good average within the United States.

The second major benefit is a shortened healing time for the donor sites, and this, of course, could be translated to a decreased mortality rate in large burns when looked at in a larger group of patients. There are several questions that arise related to this second observation. First, was there an effect on cosmetic appearance? Dr. Pruitt has also asked whether there might be an adverse effect on cosmetic appearance, especially in the healed burn and in recropped donor sites. Second, was there better take of the skin grafts, or do you think there will be based on the information so far? Finally, I would like to ask the same question that Dr. Wilmore asked. Was there a correlation of healing time with IGF-I blood levels for individual patients?

I was somewhat concerned about the effect of nutrition because nutrition has been shown by many investigators now to have a very important role in outcome in burn patients.

I noted that the treated group received about 10% fewer calories than the placebo group. This could account for some of the results, but also it may be a result of lesser need with better utility of nutrients, and I wondered if Dr. Herndon would comment on this.

There are other concerns about the use of growth hormone in humans, which I hope will be addressed in future studies. These include the question of whether antibodies against human growth hormone will develop in a population of patients already prone to the autoimmune phenomenon.

Also, will the use of growth hormone alter pituitary function and have a long-term effect on growth? And third, will there be a long-term effect on the cosmetic result, which is now becoming one of the major concerns in burn care?

Future studies with long-term follow-up are warranted, and we look forward to Dr. Herndon's continuing contributions to this field.

DR. JOHN BORDER (Buffalo, New York): You are all talking about the cost of in-hospital care. When you look at the cost of accidental injuries, in-hospital care is 15% to 25% of the total and out-of-hospital is 75% to 85%.

The primary problem with out-of-hospital care in getting the patient back to work is loss of muscle mass. It is true of all trauma.

Dr. Herndon, do you think you have evidence that we might decrease the loss of muscle mass that occurs with accidental injury and thereby reduce the cost of out-of-hospital care?

DR. JAMES C. THOMPSON (Galveston, Texas): As you look at the curves for the small dose and the large dose treatment, you realize that Dr. Herndon and his colleagues have established the level of sensitivity in these patients, but not yet necessarily established the optimal dose. I think Dr. Alexander's prediction that we will get antibodies is certainly true, so that it may be important to give large doses early and achieve an optimal result.

There are ways to modify the duration of activity or the circulating half-life of any peptide, and those maneuvers also could be tried. This is an important contribution.

DR. JOHN C. MCDONALD (Shreveport, Louisiana): Dr. Mannick, I wonder if Dr. Herndon would comment on what effect, if any, the growth hormone had on the acceptance or survival time of skin allografts.

DR. DAVID N. HERNDON (Closing discussion): Dr. Wilmore, as usual, has given a more stimulating discussion than my presentation, and I thank him for it. I do, indeed, join him in complimenting Dr. Soroff's pioneering work in this area, as well as his and Dr. Pruitt's.

In terms of correlation of IGF-I levels to healing in individual patients, we do indeed have a positive correlation between wound healing and the individual elevations in IGF-I levels. That is, those patients who have the greatest IGF-I response to the growth hormone dose of 0.2 mg/kg/day heal the most quickly.

Dr. Thompson's question about the dosing is extremely pertinent. We administer these patients 0.2 mg/kg in the morning, and as most of you know, growth hormone is usually released in the evening in normal cycles. A twice-a-day schedule or a larger dose given in the evening to achieve an optimum dose range may be more appropriate.

The question in regard to long-term cosmetic results will have to wait for completion of a longitudinal study that we are performing evaluating formation of hypertrophic scar, muscle strength, and delays in growth over time.

The questions regarding nutrition can be answered easily in that the patients in the placebo-treated group were hospitalized longer so they received more calories during the entire hospitalization, but the daily amount of calories adjusted per percentage of total body surface-area burn were indistinguishable between the two groups, but if the one group stays in the hospital longer, they will have a larger total caloric intake.

The total mean substrate intake was not less for controls on a per-burn surface-area basis.

The question regarding hypothyroidism is pertinent and very interesting. We did show a correlation of the T-4 regression with IGF-I levels. None of our patients were truly hypothyroid, but there was a positive correlation between the T-4 and IGF-I levels.

The observations about increased collagen deposition in sponge does make us considerably worried about hypertrophic scar formation, but we have as yet not seen that as a major problem. I think the reason that the donor-site healing accounts for only one half of the decrease in length of hospital stay is, indeed, that there is an increase in skin graft take and that there is an increase in the rate of healing of second-degree areas in these patients. I do not have a positive way of addressing that without studying a series of patients that is quite a bit larger than the current series.

There were no deaths and there was no morbidity specifically in this group. There was no difference in septic episodes. A much larger group would need to be used both to address the questions longitudinal analysis and muscle strength and the longitudinal analysis of scar formation in these patients.

Cystic Tumors of the Pancreas

New Clinical, Radiologic, and Pathologic Observations in 67 Patients

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Within a 12-year period we treated 67 patients (49 women, 18 men; mean age, 61 years) with cystic neoplasms of the pancreas, including 18 serous cystic adenomas, 15 benign mucinous cystic neoplasms, 27 mucinous cystadenocarcinomas, 3 papillary cystic tumors, 2 cystic islet cell tumors, and 2 cases of mucinous ductal ectasia. Mean tumor size was 6 cm (2 to 16 cm). In 39% the patients had no symptoms, and in 37% the lesions had been misdiagnosed as a pseudocyst. Computed tomography was useful for detection, for distinguishing the microcystic subgroup of serous cystadenoma, and for showing rim calcification (all 7 cases were malignant) but was not reliable for distinguishing neoplasm from pseudocyst, serous from mucinous tumors, or benign from malignant. Arteriography showed hypervascularity in 4 of 10 serous adenomas, 3 of 11 mucinous carcinomas, and 1 of 1 papillary cystic tumors. Endoscopic pancreatography showed no communication with the cyst cavity in 37 of 37 cases of cystic neoplasms but opacified the ectatic ducts in 2 of 2 cases of mucinous ductal ectasia. Stenosis or obstruction of the pancreatic duct indicated cancer. The tumor was resected by distal pancreatectomy in 25 patients, by proximal resection in 29, and by total pancreatectomy in one, with no operative deaths. Forty-four per cent of the tumors were malignant. In 10 cases the tumor was unresectable because of local extension or distant metastases, and those patients died at a mean of 4 months. Seventy-five per cent of those resected for cure are alive without evident recurrence. Because the epithelial lining of the tumor was partially (5% to 98%) absent in 40% to 72% of cases of the major tumor types, and the mucinous component comprised only about 65% of mucinous cystadenoma lining, misdiagnoses on frozen and even permanent sections were made. Mitoses and histologic solid growth correlated with malignancy. Neuroendocrine elements were seen in 87% of benign and 47% of malignant mucinous tumors. It is recommended that the terms macrocystic and microcystic be abandoned in favor of the histologic designations serous and mucinous. Incomplete examination of the cyst wall can be misleading, however. It is suggested that mucinous ductal ectasia be recognized separately from cystic tumors and that all of these lesions be resected, with the possible exception of asymptomatic confirmed serous cystadenomas.

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COMMON LORE CONCERNING cystic tumors of the pancreas is that they are rare,[1-8] potentially malignant,[3,5,6,8-10] but easily cured[5,7] or at least indolent,[3] and distinguishable from pseudocysts by biopsy of the cyst wall (which will show an epithelial lining).[4] Since the landmark papers of Compagno and Oertel in 1978,[2,3] it has been customary to distinguish microcystic (glycogen-rich serous) tumors from macrocystic (mucinous) tumors, a crucial point in that the former are universally benign[2,4,5] whereas the mucinous neoplasms all are frankly malignant or premalignant.[3,5,7,8-10] Since then there has been new recognition of two additional distinct entities, papillary cystic tumors[11-13] and mucinous ductal ectasia,[14,15] which probably have been erroneously included in earlier groupings. It also has been reported that computed tomographic (CT) scanning[16-18] and angiography[4,10,16,19] can differentiate between the microcystic and macrocystic varieties and that endoscopic pancreatography (ERCP) is not helpful in the differential diagnosis of cystic tumors from pseudocysts because even the tumors may communicate with the pancreatic duct.[20-22]

Despite the recent increased attention to pancreatic cystic neoplasms, there continues to be inadequate appreciation of the different types of cystic tumors and of the diagnostic and therapeutic approaches and pitfalls concerning them. As just one aspect of this, fully one third of the patients we see have been given the previous diagnosis of pseudocysts and many were inappropriately treated as a result.[23] In depicting our comprehensive experience with 'cystic tumors,' we will emphasize the difficulties in achieving a certain diagnosis without resection,

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TABLE 1. *Criteria for Differential Diagnosis of Pancreatic Cystic Lesions*

Method	Finding
CT	Unilocularity *vs.* multilocularity, size of cysts, solid components, presence and form of calcification.
Angiography	Tumor vessels, hypervascularity vs. hypovascularity
ERCP	Communication with cystic element, pancreatic duct distortion or obstruction
Percutaneous aspiration	Cytology, amylase, CEA, CA 19-9
Cyst wall biopsy	Presence and type of epithelial lining

CT, computed tomography; ERCP, endoscopic pancreatography.

TABLE 2. *Pancreatic Cystic Tumors (Massachusetts General Hospital, 1978 to 1989)*

Histologic Diagnosis	No.
Serous cystadenoma	18
Mucinous cystic neoplasm	15
Mucinous cystadenocarcinoma	27
Papillary cystic tumor	3
Cystic islet cell tumor	2
Mucinous ductal ectasia	2
Pseudocyst	1

the dangers inherent in the malignancy of many of these tumors, and the opportunities for cure.

Materials and Methods

Sixty-eight patients with cystic lesions of the pancreas have been evaluated and treated by our group at the Massachusetts General Hospital in the last 12 years. Included were all patients found to have a cystic neoplasm or who were operated on and resected because of that presumed diagnosis. Excluded are all patients whose cystic lesions were known to be pseudocysts or that were determined to be pseudocysts before resection. In each case the clinical history was obtained from hospital and office records. The principal techniques and criteria used in differential diagnosis are summarized in Table 1.

All pathology specimens were reviewed by a single pathologist using three gross and 17 histologic variables. The diagnostic categories were designated as serous cystadenoma (glycogen-rich adenoma, 'microcystic' adenoma),[2,4,9,24,25] mucinous cystic neoplasm (mucinous cystadenoma, 'macrocystic' adenoma),[3,7–10] mucinous cystadenocarcinoma, papillary cystic tumor (papillary and cystic neoplasm, solid and papillary neoplasm),[11–13] cystic islet cell tumor,[26] mucinous ductal ectasia,[14,15] and pseudocyst.

Gross parameters included maximum transverse diameter, location, and loculation (unilocular or multilocular, size of loculations). Multiple hematoxylin and eosin-stained sections of each tumor were examined to estimate the percentage of the tumor cyst lining that was denuded of epithelium. The percentage of the remaining epithelium containing mucin-secreting cells was scored as 0, less than 25%, 25% to 75%, or more than 75%. Neuroendocrine components were confirmed by immunoperoxidase stains.

Results

There were 68 patients, 49 women and 19 men, with a mean age of 61 years. Fifteen patients (14 women) were younger than 50 years. Thirty-three tumors were located in the head of the pancreas and 35 in the body or tail. The histopathologic diagnoses are shown in Table 2. In 67 of 68 patients, the final diagnosis was neoplasm. The one pseudocyst was a 2-cm lesion in the pancreatic head of a patient with jaundice and no pain or history of pancreatitis or alcoholism.

Table 3 correlates the clinical characteristics with each tumor type. Note the general overlap of age groups, female predominance, and size and location of the various tumors. In most instances tumor type could not be discerned by gross appearance. Although many small (1 to 5 mm) loculations in a honeycomb or sponge pattern are characteristic of the microcystic form of serous cystadenoma, this accounted for only one fifth of these cases. In the rest of the serous cystadenomas and in all of the other tumors, the range of the loculation sizes was similar (1 to 16 cm) and was not a distinguishing feature. Thirty-nine per cent of patients with benign lesions had no symptoms; their tumors were found incidentally because of a palpable mass or on a scan performed for other purposes. Two of 38

TABLE 3. *Clinical Characteristics of Pancreatic Cystic Tumors*

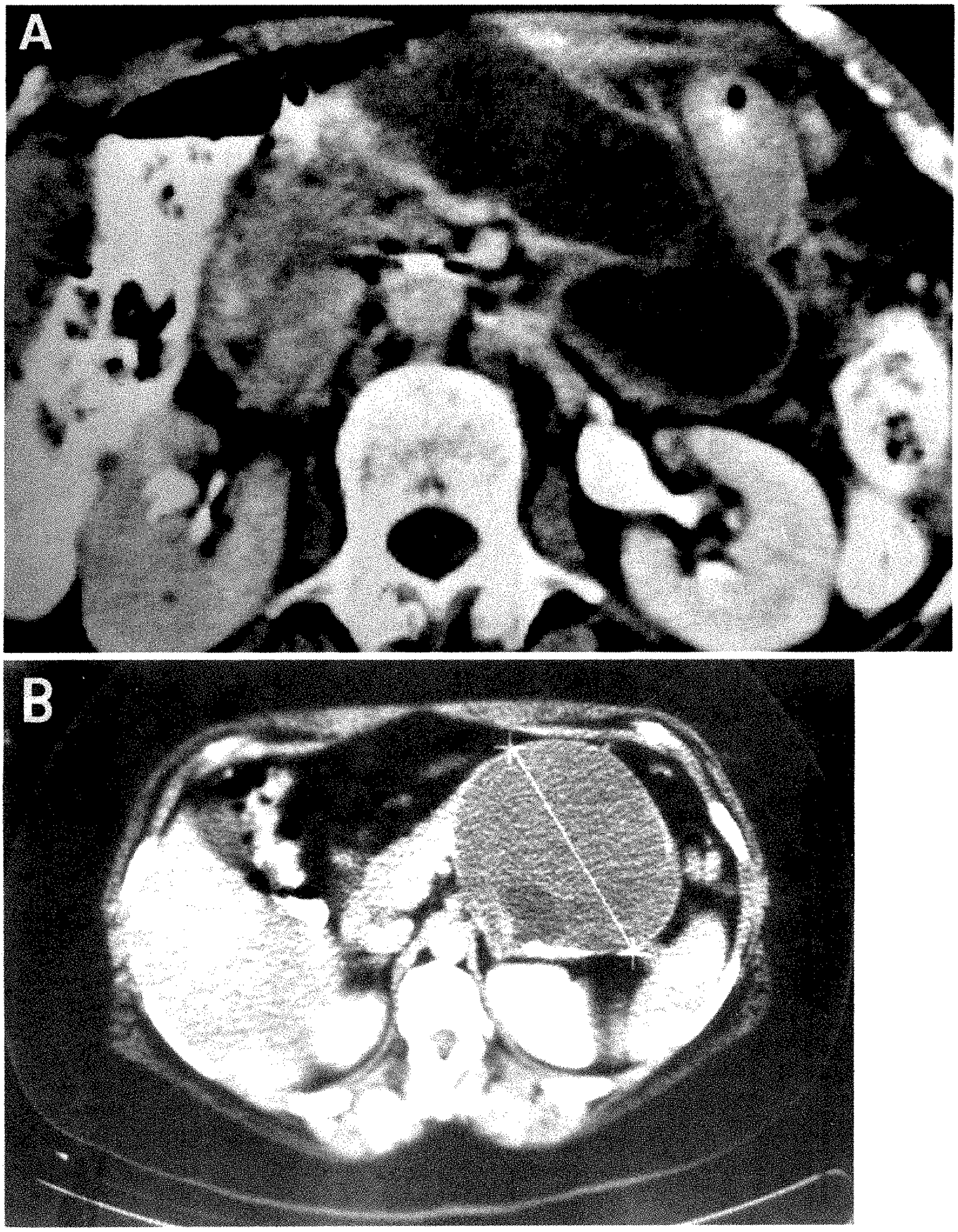
Type	Mean Age (years)	Female (%)	Pancreatic Head (%)	Mean Size (cm)	Symptoms (%)	Pseudocyst mis-dx (%)
Serous cystadenoma	64	72	39	5	56	33
Mucinous cystic neoplasm	59	81	47	5	60	40
Mucinous cystadenocarcinoma	63	74	56	6	85	41
Papillary cystic tumor	44	67	13	8	67	33
Cystic islet cell tumor	60	50	0	5	50	0
Mucinous ductal ectasia	69	0	100	6	100	50

benign tumors presented with jaundice and three with pancreatitis. Among 30 patients with malignant tumors, only 15% were not symptomatic, and five presented with jaundice.

In 13 instances the patient also had a separate cancer concurrently or previously. Those were located in the pancreas (2), bile duct (1), urogenital tract (6), or other locations (4).

In 25 cases the patient had been assigned a diagnosis of pseudocyst. This resulted in cyst-enteric anastomoses (7 cases), percutaneous needle or catheter drainage (4 cases), and prolonged observation for 1 to 8 years. In four cases tumor that was resectable (but not resected) at first operation was metastatic and unresectable at reoperation.

Computed tomographic and ultrasound scans, performed in 65 cases, were excellent tools for detection of cystic tumors. At least 15 cases were identified because of incidental discovery on scans performed for other reasons. Loculations often were detectable but frequently were inapparent when the septae were delicate. The pres-

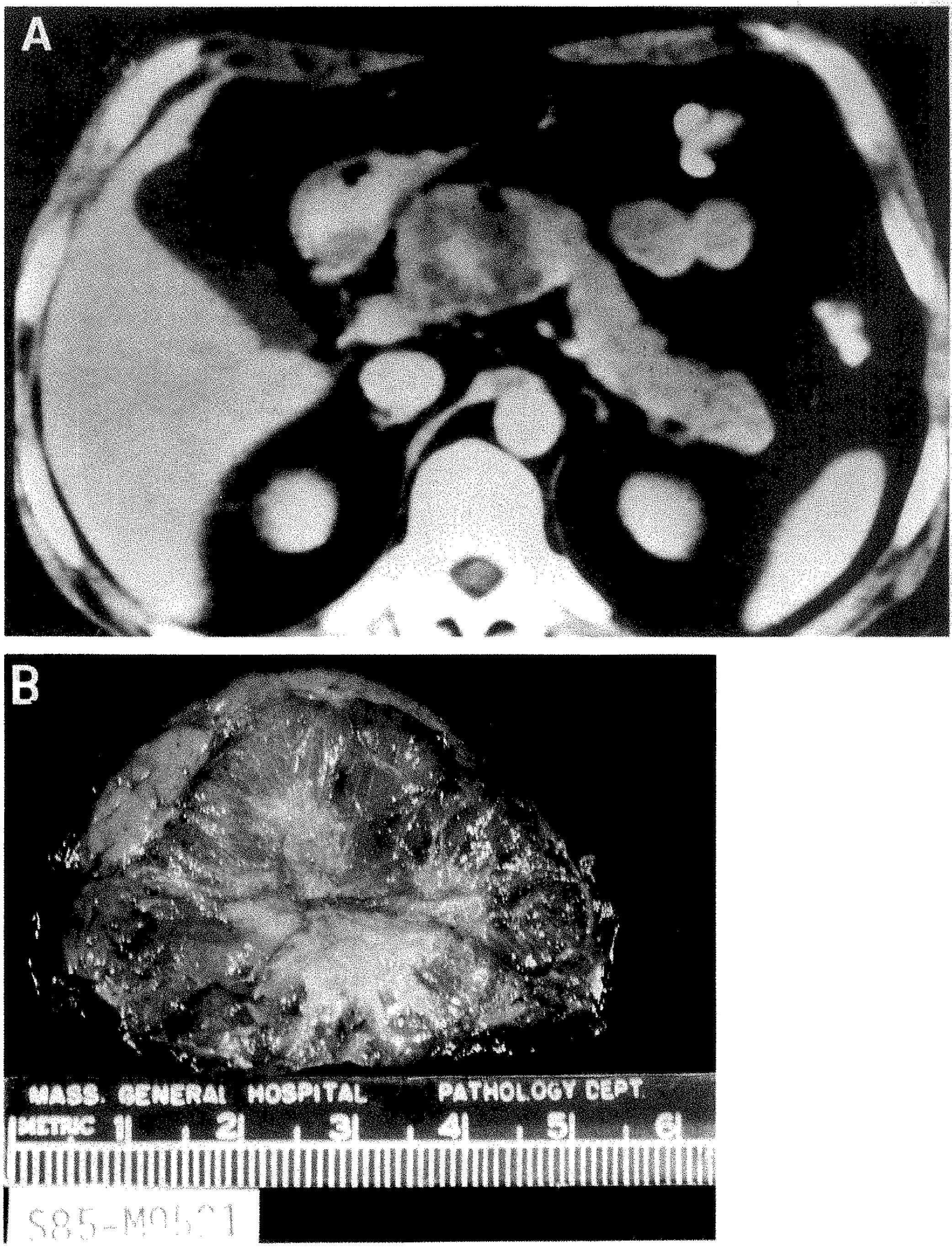


FIGS. 1A and B. Computed tomographic scans showing two serous cystadenomas, one with a septum (A) and one that appears to be unilocular (B).

ence of loculations proved to be a reliable criterion for neoplasm (as opposed to pseudocyst) but were unreliable for differentiating serous from mucinous tumors (Fig. 1). So-called microcystic adenomas (all serous) were identifiable by CT when multiple small loculations were apparent, but this occurred in only 50% of serous cystadenomas. The central scar and sunburst calcification, which are said to be highly suggestive of microcystic adenomas, were seen in only 2 of 18 cases (Fig. 2).

A solid component to the tumor was identifiable in some instances but not in others (Fig. 3). Often the solid components were too small to be resolved by CT. Unless there was considerable solid tumor (Fig. 4) or liver metastases, CT was ineffective in distinguishing benign from malignant macrocystic lesions. An estimation of local resectability could be made with fair reliability, but liver and peritoneal metastases were missed in five cases.

Localized calcifications were common (30%) and oc-



FIGS. 2A and B. Computed tomographic scan showing a central sunburst calcification (A), correlating with the central scar in a microcystic adenoma (B).

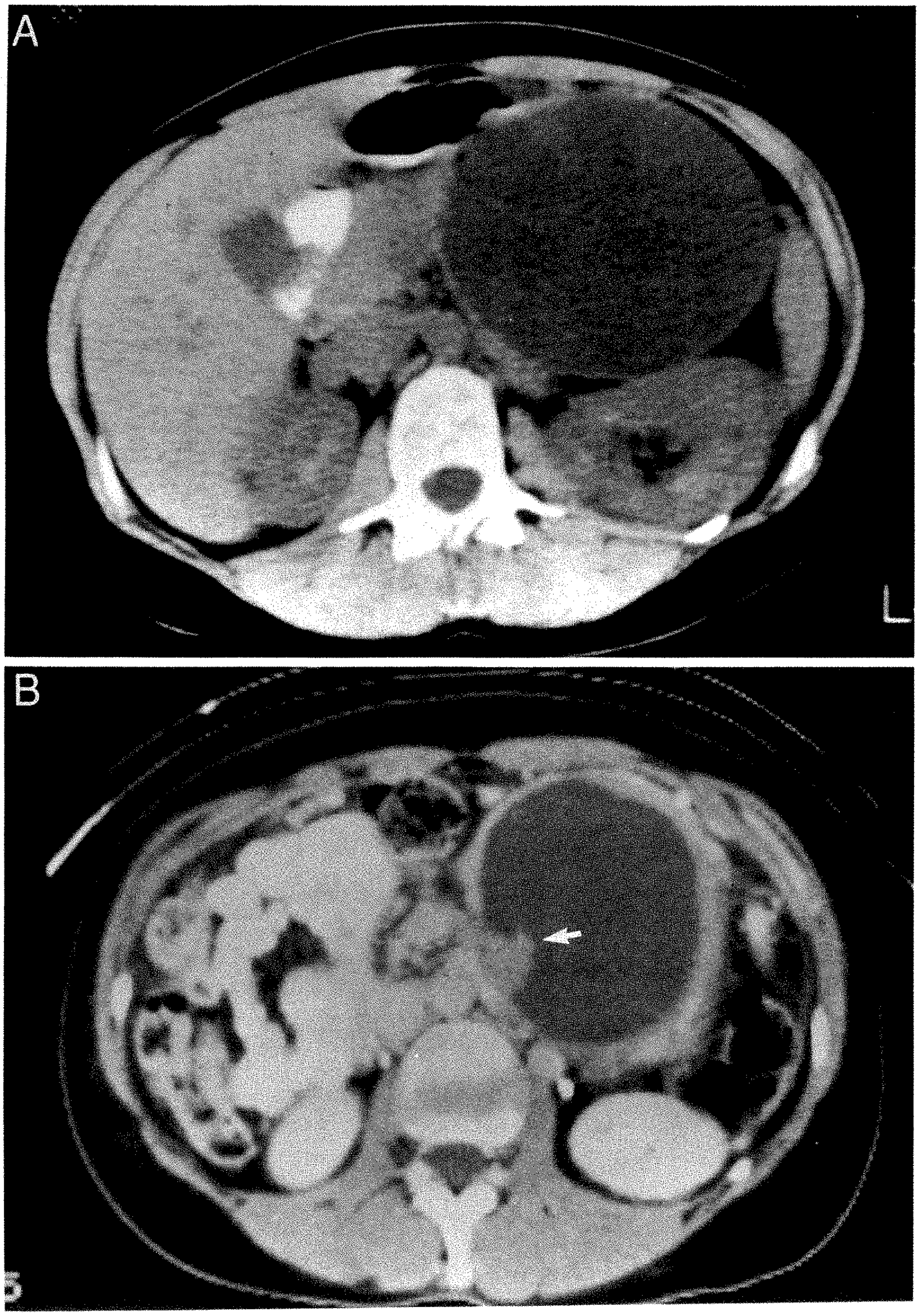


FIG. 3. Computed tomographic scans of two mucinous cystadenocarcinomas. Solid excrescences were present within the cyst cavities of both but were visible on scan in only one (arrow).

curred nonspecifically in each of the tumor types. A peripheral rim of calcification (Fig. 5) was noted in seven tumors. Surprisingly all were cancerous: six mucinous adenocarcinomas and one malignant papillary cystic tumor.

Endoscopic pancreatography (ERCP) was performed in 40 cases (Table 4). In 38 of 40 patients there was no communication demonstrated between the pancreatic duct and the cyst cavity (including the pseudocyst). Distortion of the duct (draping or bowing over a large tumor) (Fig. 6) was seen in 14 cases. Three ducts were constricted

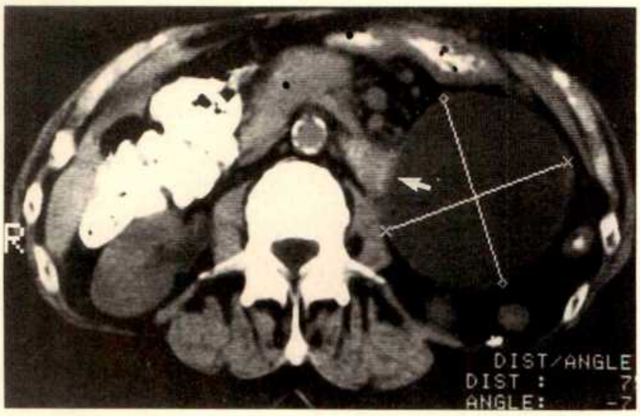


FIG. 4. Computed tomographic scan of an unresectable mucinous cystadenocarcinoma. A component of solid tumor is seen to the left of the cyst (arrow). Cytologic examination of a percutaneous aspirate showed malignant cells.

and four ducts were completely obstructed (Fig. 7) among 17 cancers.

Celiac and superior mesenteric angiography was performed in 27 cases. Hypovascularity (negative impression due to splaying of vessels) was seen in 19 cases. Hypervascularity (said to be characteristic of microcystic adenomas) was present in only 4 of 10 serous cystadenomas (Fig. 8), and was also seen in 3 of 11 mucinous adenocarcinomas and 1 islet cell tumor (Table 5).

Aspiration of the cyst cavity was performed too infrequently to make broad comments. In six of six cases, the amylase content was low. In four mucinous tumors, mucinous cells were identified on cytologic study and two of those had cytologic characteristics of malignancy.

Operations were performed on 65 patients: 25 distal (body and tail) resections, 29 proximal pancreatoduodenectomies, 1 total pancreatectomy, and 10 explorations with biopsy of cancer unresectable because of local extension (9) or distant metastases (6). There were no postoperative deaths. One patient with a postoperative infected mucinous fistula was not fit for reoperation after a previous cyst duodenostomy, and two are awaiting operation. Noteworthy was a marked desmoplastic response seen around the tumor in a number of instances. This dense fibrotic reaction made separation of the lesion from surrounding structures, such as the mesocolon, colon, and duodenum, very difficult and raised concerns about invasive cancer. In one case the transverse colon was removed with the tumor on this account. Unless there were metastases or grossly invasive cancer, usually it was impossible for the surgeon to distinguish between tumor types or to determine whether the tumor was malignant (Fig. 9).

The distribution of histopathologic diagnoses is shown in Table 2. Note from Table 3 that the mean cystic tumor size is the same in all groups but also that there is overlap at all points on the spectrum of loculation size. Both serous and mucinous cysts ranged in size from 2 to 16 cm and could be unilocular or multilocular. Similarly the ranges of benign and malignant cysts are similar. Only the microcystic honeycomb pattern was purely serous.

Histologic examination (Table 6) showed an incomplete (denuded) epithelium in 40% of serous cystadenomas and 72% of mucinous tumors (benign or malignant). The area of absent epithelium averaged 40% of the wall (up to 98%) in the denuded tumors. This phenomenon led directly to errors in diagnosis on microscopic examination of both frozen and permanent sections until the entire specimen was examined on review.

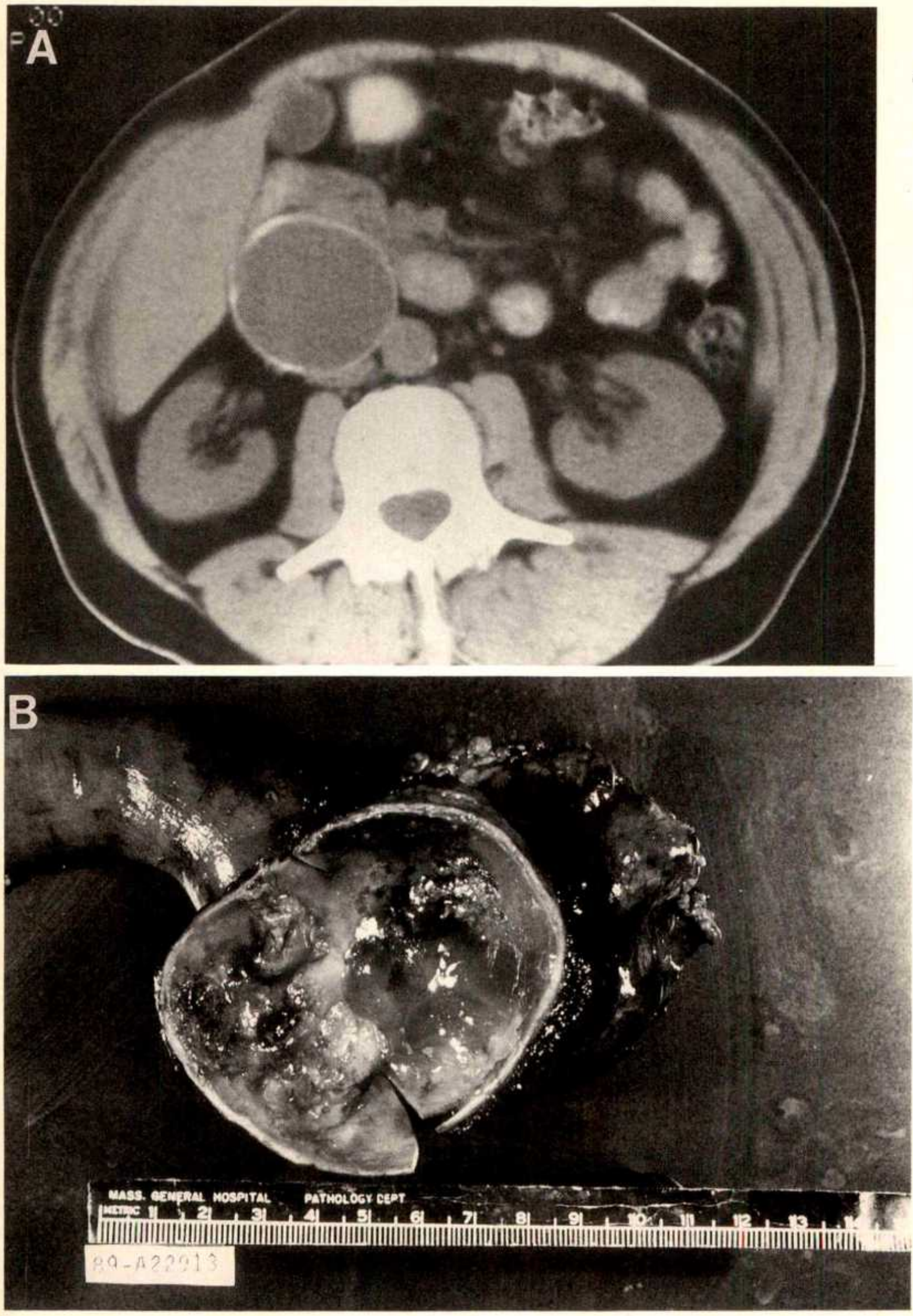
Mucinous tumors were found not to be uniformly composed of mucinous epithelium. Among benign mucinous neoplasms, mucinous epithelium covered an average of about 65% of wall area (67% of cases were less than 75% mucinous). Among malignant mucinous tumors, 89% of cases were more than 75% mucinous. Mucinous epithelium accounted for 25% to 75% of all three papillary cystic tumor linings but was not found in any serous cystadenoma. Because of the nonuniformity of the mucinous component, errors of classification were made on initial examination in three cases.

Neuroendocrine cells were noted (and confirmed by immunoperoxidase stains) in 87% of mucinous cystic neoplasms and 47% of mucinous cystadenocarcinomas (and in all three islet cell tumors, of course). An endocrinopathy was apparent in only one patient, who had a duodenal gastrinoma along with a serous cystadenoma of the pancreatic body.

Mitoses were found in 88% of mucinous cystadenocarcinomas, in one of two malignant papillary cystic tumors, and in the malignant mucinous ductal ectasia. No mitoses were found in any serous cystadenoma or in any benign mucinous cystic neoplasm.

Histologic solid growth (foci in which cells piled up in 'solid' fashion without individual cell contact with the basement membrane) was not found in any serous cystadenoma but was present in all of the other tumor varieties. In the mucinous series, solid growth was present in 8% of benign tumors and in 88% of malignant tumors.

Clinical and histopathologic evidence of malignancy was found in 44% of the tumors in this series (Table 6). This occurred in 27 of 42 of the mucinous series, 2 of 3 of the papillary cystic tumors, 1 of 2 of the mucinous ductal ectasia, and in none of the serous cystadenomas. We expect that some islet cell tumors will be malignant, but the sample size (2) in this collection is small. Only 63% of the mucinous adenocarcinomas were judged to be clearly resectable. Of the latter one patient had a positive resection margin (and died of cancer) and another



FIGS. 5A and B. Computed tomographic scan showing calcification of the rim of a pancreatic cyst (A). Despite the apparently smooth walls, the opened specimen contained excrescences of carcinoma (B).

had a positive adjacent lymph node (and remains free of disease at 2 years). Overall 13 of 17 resectable mucinous cancer patients (76%) are alive without evident recurrence (48% of all mucinous cancers) at 6 months to 10 years. All deaths in the group resected for cure occurred within 15 months of resection. Twenty-two per cent of the mucinous cystadenocarcinomas had nonlocal metastases. All patients with unresectable local or metastatic cancer died at an average of 4 months. The man patient with papillary cystic carcinoma died with recurrence at 4 years, but the

TABLE 4. *Endoscopic Pancreatography in Pancreatic Cystic Tumors*

Type	No.	Communicating	Draped	Constricted	Obstructed
Serous cystadenoma	8	0	4	0	0
Mucinous cystic neoplasm	9	0	6	0	0
Mucinous cystadenocarcinoma	17	0	3	3	4
Papillary cystic tumor	3	0	0	0	0
Mucinous ductal ectasia	2	2	2	0	0
Total	39	2	15	3	4

woman is well at 5 years. The mucinous ductal ectasia contained an *in situ* cancer and the patient is well.

Discussion

Cystic neoplasms of the pancreas are thought to be rare, perhaps accounting for 10% to 13% of 'pancreatic cysts' and 1% of pancreatic cancers.[1,27] Our experience indicates a far greater frequency, which was partly influenced by the concentration of cases at our institution but also due to corrected identification of neoplasms previously diagnosed as pseudocysts. The differential diagnosis of a cystic lesion of the pancreas must include a variety of neoplasms, particularly in the absence of antecedent factors or events that could generate a pseudocyst. Irregularity or loculation in the cyst or a solid component when present indicate a tumor, but their absence on scan is not unusual.[4,17] Failure to be alert to the possible presence of tumors, especially in young women, too often leads to errors in treatment.[23,26] Mucinous cystic neoplasms of the pancreas are likely to develop in patients with Von Hippel-Lindau disease.[4,28]

While identification of a cystic tumor is relatively easy (we included only one pseudocyst erroneously in our preoperative diagnoses in this series) the identification of the specific tumor type may be difficult because of overlapping of characteristics: most occur in middle-aged women (14 younger than 50 years), have a mean diameter of 5 to 6 cm, and may present with pain, pancreatitis, or no signs. To the six species of tumor found in the present series could be added lymphangiomas, hemangiomas, and high-grade ductal cancers that can partially liquefy because of central necrosis.

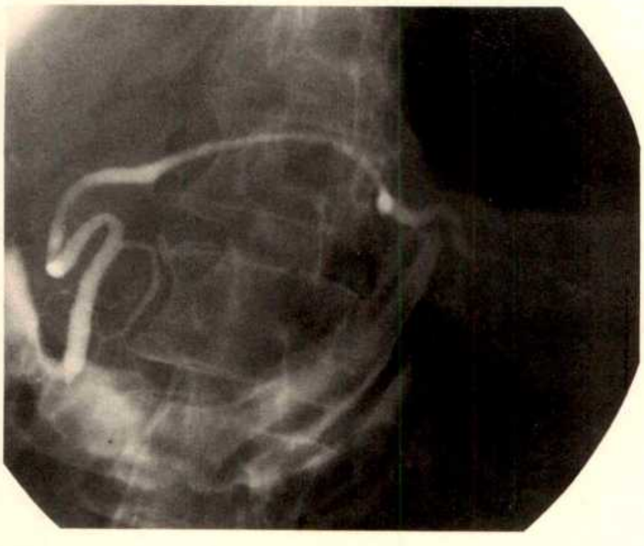


FIG. 6. Endoscopic pancreatogram showing distortion of the pancreatic duct by a tumor over which it is draped.

Certain physical characteristics proved helpful in diagnosis. Whereas size and location of the lesion were of no value, loculation and solid components on scan are reliable indices of neoplasm. The appearance of a loculated neoplasm generally differs from that of multiple pseudocysts in that the septae are more delicate, the cysts more coalescent, and the locules often irregular in shape.[16–18] Calcification is common in cystic tumors[16,18] but we have not seen it in the wall of pseudocysts, albeit calcifications in the pancreas are commonplace in chronic pancreatitis. Calcification of the rim of the cyst wall,[13,16] either as a crescent or as a complete circle, was seen in seven cases; to our surprise all were malignant. This phenomenon perhaps attests to the long natural history of some cystic tumors, especially those undergoing malignant degeneration. The central 'sunburst' calcification of some serous cystadenomas is characteristic and highly suggestive of that particular entity[16] but occurred in only 11% of our cases and has been said to be exceptional.[17,29] Hypervascularity on arteriographic examination indicates a neoplasm, but not its type. While said to be characteristic of the 'microcystic adenoma,'[19,29] we found that to be true in only 40% of serous cystadenomas and also to occur in 33% of mucinous adenocarcinomas.

Endoscopic pancreatography was helpful primarily in indicating some cases of cancer. In 50% of all studies the pancreatogram was normal; in 33% there was nonspecific bowing around the mass; but in cancers there was stenosis or occlusion in 18% and 24%, respectively.

It has been suggested that pancreatography could be useful in distinguishing cystic tumors from pseudocysts in that the pancreatic duct can be shown to communicate with 70% of pseudocysts,[30] but a neoplastic cyst ought to

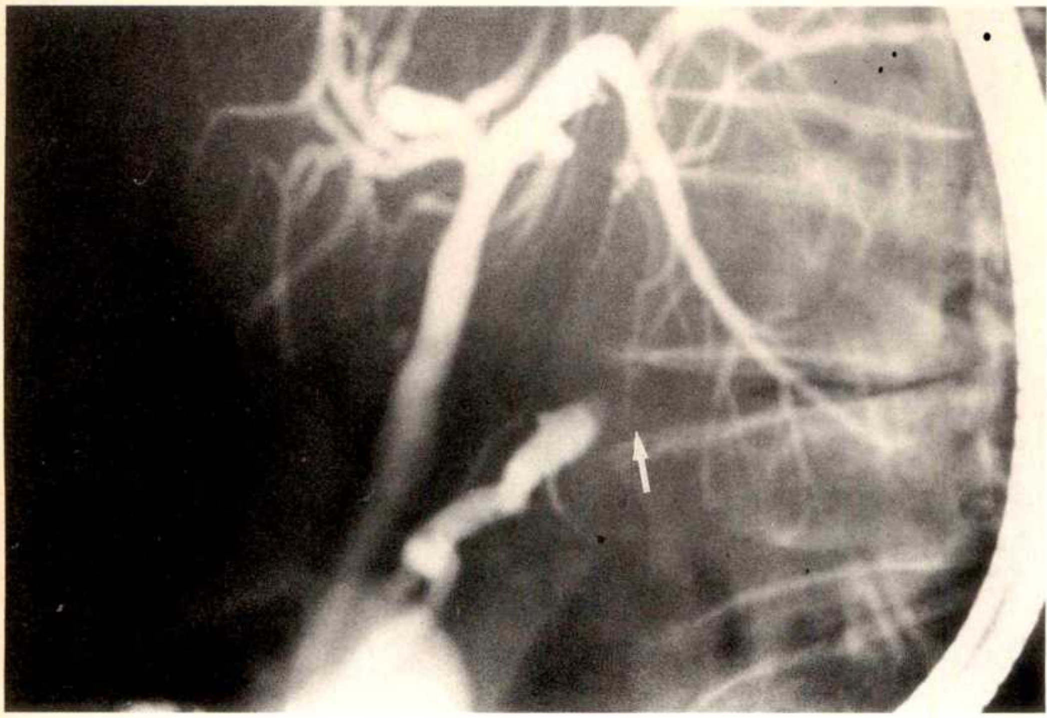


FIG. 7. Endoscopic pancreatogram showing complete obstruction of the pancreatic duct (arrow) by a mucinous cystadenocarcinoma. The biliary tree is also opacified.

be separate.[23] Although there are a few anecdotal reports of single examples of opacification of a cystic tumor at ERCP,[20–22] most reports are of absence of communication, and we had no instance of communication in pancreatograms performed in 37 patients with neoplastic cysts. Other than the possibility that an occasional neoplastic cyst may have a communication with the pancreatic duct, we suggest two possible alternative explanations for the previously reported observations: (1) the cavity filled at pancreatography was, in fact, an associated pseudocyst

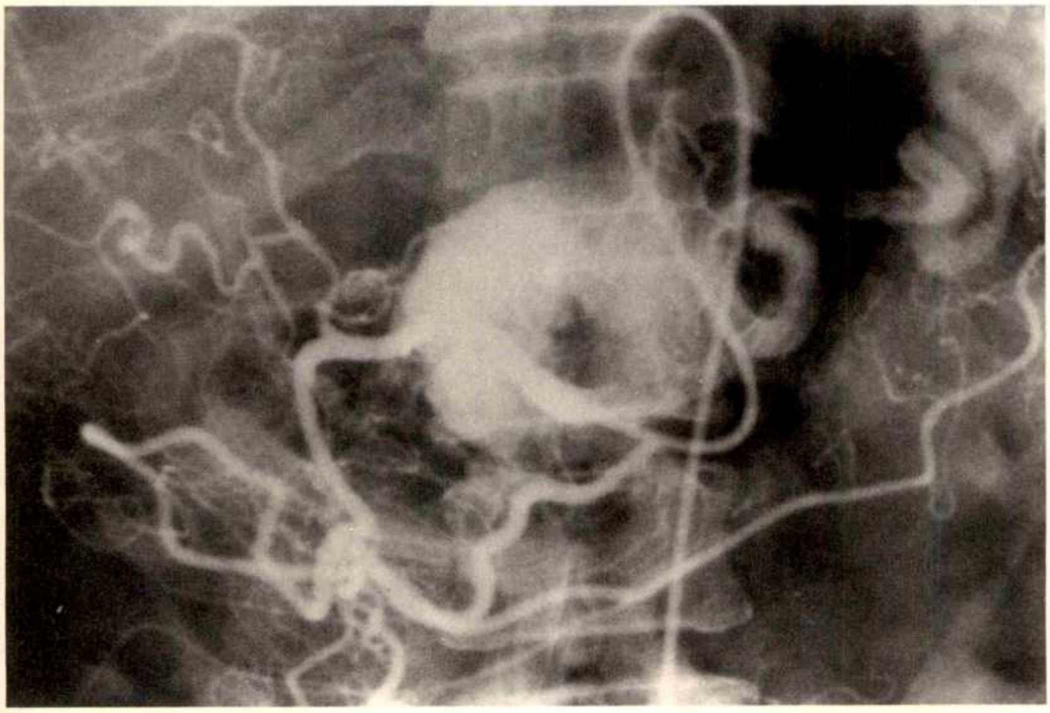


FIG. 8. Celiac arteriogram showing a hypervascular serous cystadenoma (same patient shown in Figure 2).

TABLE 5. *Angiography in Pancreatic Cystic Tumors*

Type	No.	Hypervascular	%
Serous cystadenoma	10	4	40
Mucinous cystic neoplasm	6	0	0
Mucinous cystadenocarcinoma	11	3	27
Cystic islet cell tumor	1	1	100
Mucinous ductal ectasia	2	0	0
(Pseudocyst)	1	0	0

arising as a consequence of obstructive pancreatitis caused by the underlying cystic tumors; and (2) the lesion studied was an example of mucinous ductal ectasia, rather than cystadenoma.

Mucinous ductal ectasia is a newly recognized premalignant lesion[14,15] in which there are papillary hyperplasia and mucin overproduction along the pancreatic duct, involving part or all of the gland and leading to obstructive pancreatitis because of mucus filling the duct. A startling experience for the endoscopist may be to see mucus exuding through the ampullary orifice[14,15] (as seen in one of our cases). Pancreatography shows filling of the dilated 'cystified' ducts along with the intraluminal mucus globs. It is clear that some previous reports have unknowingly included mucinous ductal ectasia cases among cystadenomas[10] and that the current literature continues to confuse the two entities,[15] which are entirely different clinically and morphologically.

Percutaneous aspiration of cystic tumors for sampling of amylase content,[23,31] CEA[32,33] or CA 19-9[34] level, and cytologic examination[10,35,36] has been reported sporadically. The number of cases is far too small to evaluate how sensitive or reliable these parameters might be. Our own sparse experience suggests that amylase content of neoplastic cysts is low (six instances)—there are two single case reports to the contrary[20,22]—and that cytologic examination of the aspirates may show mucinous cells or cytologically malignant cells (one case each). Percutaneous sampling of the cyst fluid deserves further consideration, limited mainly by the concern that malignant cells could potentially be spilled and seeded.

The irregularity of the tumor cyst epithelium is a prominent feature of many of these tumors[3] and merits a strong caveat. It occurred in 40% of the serous cystadenomas and 72% of the mucinous tumors and involved an average of 40% (up to 98%) of the cyst wall area. In fact this led to initial diagnoses as pseudocysts in four cases, errors that were corrected only with careful review of additional tissue sections from other areas of the tumor. It seems very likely that others have also fallen into this trap. Of incidental note, we wonder whether the intense desmoplastic response found around some mucinous neoplasms might be caused by transmural passage of irritating cyst contents through areas of cyst wall without an epithelial barrier.

Similarly the mixed nature of the epithelium of the mucinous tumors could lead to errors in diagnosis. Whereas the serous cystadenomas had uniform serous epithelium, the benign mucinous neoplasm contained an average of 65% mucin-producing cells (as little as 5%), but most of the other cells were serous. Nonetheless it is the mucinous component that is the important determinant because malignant degeneration occurred only in this portion. In tumors containing both benign serous and mucinous areas, cancer was seen to arise always from the latter. Because the gross appearance of most of the cystic tumors is generally similar and, with the exception of the microcystic variety of serous cystadenoma, loculation size may not be different, the diagnostic impression of the surgeon is also subject to error.

It is believed that the duct cell is the progenitor of mucinous neoplasms of the pancreas.[9,27] Because the neuroendocrine cells of the pancreas are now thought to have a similar origin, it is not surprising to find neuroendocrine-type cells in so many of the mucinous tumors.[37] Our studies with immunoperoxidase stains for specific hormones will be presented elsewhere, but there was no clinical evidence of endocrinopathy in these patients, with the exception of one who has a simultaneous duodenal gastrinoma. Whether the cystic islet cell tumors should be considered true relatives of the mucinous cystic neoplasms is undetermined.

Generally it is accepted that pancreatic cystic tumors with serous epithelium are not and do not become malignant[2,4,8,9] but that all of the other cystic tumors are either malignant or have the potential for malignant degeneration.[3,4,5,7–15] Compagno and Oertel[3] emphasized the difficulty of the histopathologic diagnoses of malignancy in the absence of local invasion or overt metastases. We

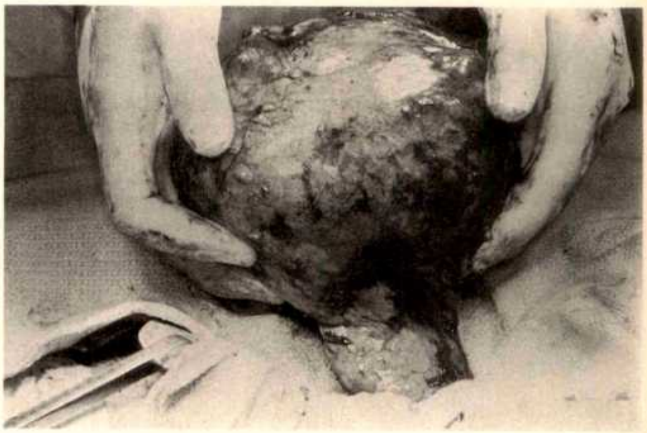


FIG. 9. Serous cystadenoma of the tail of the pancreas (same patient shown in Figure 1).

TABLE 6. *Histopathologic Findings in Pancreatic Cystic Tumors (% of total in group)*

Type	Calcification	Rim Calcification	Denuded	Neuroendocrine Elements	Mitoses	Solid Growth
Serous cystadenoma	30	0	22	0	0	0
Mucinous cystic neoplasm	13	0	75	87	0	8
Mucinous cystadenocarcinoma	33	22	69	47	88	89
Papillary cystic tumor	67	33	0	0	33	100
Cystic islet cell tumor	0	0	0	100	0	100
Mucinous ductal ectasia	100	0	0	0	50	100

have found mitoses in 84% of known malignant tumors and in none of the apparently benign tumors. The histologic characteristic of solid tumor cells growth (cells piled up without contact with the basement membrane) was almost as reliable an index because it was found in 88% of mucinous cystadenocarcinomas but also in 8% of otherwise benign mucinous cystic neoplasms. It is possible that solid growth is a histologic index of incipient or early malignancy.

It is frequently stated that cystadenocarcinomas of the pancreas are highly curable.[3,5,7,9] Most are said to be resectable,[7,8] and cure rates of 70% are quoted for mucinous cystadenocarcinoma.[7,8] Remine et al.[6] of the Lahey Clinic pointed out that the widely cited series from the Mayo Clinic reported by Hodgkinson et al.[7] contained a disproportionate number of low-grade tumors (20 pf 21 were grade 1 or 2). In their own study Remine et al.[6] found that 8 of 11 patients with mucinous cystadenocarcinoma had a highly dysplastic aggressive cancer and already had metastases at the time of operation. Their findings implied two distinct populations of mucinous cancers: those with good tumors (none of these patients died of cancer when the lesion was curatively resected) and bad tumors (eight patients with metastases died rapidly). The latter contradicts the wildly accepted statement by Compagno and Oertel[3] that the prognosis of unresectable mucinous adenocarcinoma is substantially better than that of the usual noncystic ductal adenocarcinoma of the pancreas. Our own experience supports that of the Lahey Clinic group. Sixty-four per cent of our mucinous tumors were malignant and 33% already had metastases; only 63% were resectable. Of those resected for intended cure, 76% are currently alive without evident recurrence (48% overall). Of those not resected or incompletely resected, all have died within a time frame similar to that of other pancreatic cancers (average, 4 months). In addition there may be an increased frequency of other cancers in these patients.[8]

Because of the extraordinary duration that some mucinous tumors have been 'safely' observed before the appearance of malignancy (up to 8 years in this series), it is accepted generally that all mucinous cystic neoplasms should be considered potentially malignant.[3-6,9] Our observations suggest that mucinous cystic neoplasms may be relatively dormant for years in a state of latent malignancy[3,38] but have the capacity to convert to high-grade aggressive cancer without warning. For these reasons, even if asymptomatic (as so many of our patients were), all mucinous cystic neoplasms should be resected: neither observation nor cyst-enteric anastomosis[6,20,23] are logical or acceptable alternatives.

Consistent with other reports, our experience with papillary cystic tumors[11-13] and mucinous ductal ectasia[14,15] suggests that these tumors frequently are malignant but are likely to be resectable and curable, despite impressive size. In two cases of papillary cystic cancers, metastases to the liver and omentum were also resected with resulting cure.[13,39]

From this experience we conclude that the cystic neoplasms of the pancreas include a variety of tumors, benign and malignant. These have shared clinical and radiologic characteristics that make preoperative distinction difficult, with the exception perhaps of the true microcystic subgroup of serous cystadenomas. In most cases it is not possible prospectively to separate with confidence the serous cystadenoma (always benign) from mucinous neoplasms (always malignant or potentially malignant). We strongly recommend that the terms microcystic and macrocystic be discarded as inaccurate and misleading, and that the exact histologic designations (serous and mucinous) be used. This means that the exact diagnosis in many cases cannot be made until the full specimen is available for study. Even at that time gross inspection and biopsy (or anything less than full histologic evaluation of multiple areas of the cyst walls) can be misleading for distinguishing pseudocysts from neoplasm, serous from mucinous, and benign from malignant.

Mucinous ductal ectasia should be recognized as a separate entity, clearly different from mucinous cystic neoplasms, arising within the pancreatic ducts rather than separate from them, and causing mucinous obturation of the pancreatic ducts with resulting obstructive pancreatitis and gland failure.[14,15] Endoscopic pancreatograms in mucinous ductal ectasia uniformly show filling of the ectatic ducts, whereas in our experience none of the 37 pancreatograms (or any of the examinations by a pathologist) showed communication between the pancreatic ducts and the cystic structures of the other tumors.

We recommend that cystic tumors of the pancreas should, in general, be resected for the relief of symptoms and for treatment of cancer. Some authors suggest that asymptomatic serous cystadenomas—the only cystic tumor that has never been malignant—can be observed safely, especially in elderly or poor-risk patients.[2,8,24] While this concept is theoretically reasonable, in practice it is difficult to determine with certainty that a given lesion is a serous cystadenoma and not one of the other, more ominous varieties. We suggest that the option of nonintervention may be safe only in those tumors that have the CT characteristics of microlocularity and the central scar with sunburst calcification. Otherwise, given the low risk of resection, it is safer to remove the neoplasm.

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DISCUSSION

DR. ROBERT E. HERMANN (Cleveland, Ohio): I would like to congratulate Dr. Warshaw and his coauthors for this outstanding review of cystic tumors of the pancreas. This is the largest and most comprehensive review by a single surgeon in a single institution's experience of which I am aware, and I am sure it will become a frequently referenced report. There is a great deal of information in the manuscript, really a wealth of detail, only some of which could be reported today, and I recommend that all surgeons who treat pancreatic disease become familiar with this paper when it is published.

In my discussion I would like to focus on one issue that Dr. Warshaw mentioned. The difficulty in distinguishing a cystic tumor from a pseudocyst. In more than one third of their patients, 37%, an erroneous diagnosis of pseudocyst previously had been made. I have seen this happen frequently and have actually done it once myself, in a patient in whom a large, solitary cystic tumor was anastamosed to the stomach because it was thought to be a pseudocyst.

I believe that there are four key features of cystic tumors that should help surgeons avoid this error. First there is usually no history of antecedent pancreatitis or trauma to the pancreas in patients who have cystic tumors. Second the CT scan will almost always show either septae, a multicystic lesion, or a solid component inside a cyst. Third at operation a cystic tumor usually has less surrounding fibrosis or scarring than the average pseudocyst does, although I was disheartened to read in Dr. Warshaw's report that some of his tumors had a quite dense fibrosis. Finally, on opening and biopsying the cyst wall, one will usually, but not always, identify the tumor. However, as Dr. Warshaw notes, some of the wall may be a fibrous reaction and only some of it may have tumor in it. So if you are suspicious that it is a tumor and resection is possible, then you should probably resect the lesion or biopsy further areas to be sure about the diagnosis.

I would like to ask Dr. Warshaw if he would comment further, now that he has reviewed this extensive series, on his indications for preoperative arteriography in patients with suspected cystic tumors and for his indications for preoperative endoscopic pancreatography. Do you think these studies are helpful in most cases, and are they cost effective in making the diagnosis or in identifying vascular patterns in those patients in whom you plan to resect a cystic tumor?

DR. CHARLES F. FREY (Sacramento, California): At the University of California, Davis Medical Center, we have had a large experience with cystic neoplasms of the pancreas, and based on that experience, I want to commend Dr. Warshaw for this outstanding report. It certainly confirms many of the biases I have based on our experience.

There are several points that Dr. Warshaw made that deserve emphasis because they affect patient management.

His observation that one third of these cystic neoplasms, 25 of 68, were previously diagnosed as a pseudocyst mirrors our own experience. Misdiagnosis often results in inappropriate operative procedures being performed and long delays before definitive operative management is instituted. As a result of delays in appropriate operative management, otherwise resectable tumors become unresectable.

Dr. Warshaw, you have delineated the CT scan, ERCP, and angiographic findings and amylase levels in the cystic structures, which are useful in differentiating pseudocysts from tumorous cystic lesions. On which patients do you recommend that these studies be performed? All patients with pseudocysts? Based on our experience, it is mandatory that all these studies be carried out in that group of patients with cystic lesions who have no history of alcoholism or other good explanation for having a benign pseudocyst.

In your patients with jaundice, did you note any in whom the tumor had fistulized into the common bile duct? We had two such patients in whom the jaundice resulted from the mucinous viscus secretions rather than mechanical obstruction by the tumor. We think surgeons should be encouraged to resect these lesions that are often large and bulky. We have noted an intense desmoplastic response initiated by these tumors. The tumor itself may be smaller than the size of the mass suggests. We encourage experienced pancreatic surgeons to attempt to resect these lesions even when they are large and bulky because there is no other good palliation possible. This may take some courage, but often results in a gratifying outcome because the tumor may be smaller than the mass itself, and not involve the margin of resection.

Dr. Warshaw, have you used chemotherapy or radiation therapy on any of these patients with malignant mucinous cyst adenocarcinomas?

DR. JOHN HOWARD (Toledo, Ohio): I rise to describe a patient with mucinous ductal ectasia.

A woman, age 55 years, presented with recent onset of steatorrhea. CT scan showed a multicystic lesion of the head of the pancreas involving the entire head of the pancreas but also a dilated duct in the tail. Whipple resection was performed without a diagnosis. She is now doing well 5 years after resection.

The histology was that of papillary projections in the duct, either malignant or highly suggestive of malignancy.

Dr. Warshaw, do these mucinous tumors express CEA and CA-19-9 out of proportion to the usual exocrine adenocarcinoma?

And finally, for the surgeon who sometimes sees a mucinous pancreatic tumor, about one half of them at the operating table will have a mucinous content that you can pick up with forceps and string like the white of an egg, and I think when you see it, it is diagnostic. It is not uniformly present.

DR. HENRY A. PITT (Baltimore, Maryland): We have been reviewing our experience with cystic pancreatic tumors at Johns Hopkins and have been wrestling with the question of whether to lump various lesions together or to separate them. Obviously you have chosen to lump many 'cystic' tumors. One of these lesions is mucinous duct ectasia. First let me confirm that this lesion does exist. In the past 4 years I have cared for two of these patients. In comparison to your two, my patients both had extensive malignant disease at the time of presentation. They were recognized at ERCP with mucous coming from a very ectatic duct, as you have described. Only one of my patients was resectable but with a positive uncinate margin. He is still alive, however, at 15 months and has received postoperative radio- and chemotherapy.

Another group that might be included with cystic pancreatic tumors are those patients with typical adenocarcinomas who present with severe pancreatitis and a pseudocyst. I wonder whether you have included any of these patients in your report and, if so, whether they should be included. Do any of the patients who you have classified as cystadenocarcinoma, but who only had a portion of the cyst epithelium with malignant change, really have adenocarcinoma of the pancreas with an associated pseudocyst?

DR. R. ROSSI (Burlington, Massachusetts): This is a timely report because we are increasingly seeing patients with incidental cystic lesions found on CT scan or ultrasound done for other reasons.

The conclusions of our recent report with 45 cases are similar to those of Dr. Warshaw and cannot be overemphasized. With the exception of a few cases in which imaging studies show a honeycomb microcystic pattern with central scarring and central calcifications, preoperative imaging techniques are not reliable in differentiating serous from mucinous tumors, benign from malignant cystic tumors, or cystic neoplasms from other neoplasias with central necrosis or pseudocysts.

The findings of chronic pancreatitis, such as pancreatic calcifications of ductal changes on ERCP, do not rule out a neoplasm because both can coexist. At operation, with the exception of the honeycomb microcystic adenoma, the surgeon frequently cannot accurately differentiate serous from mucinous tumors or benign and malignant tumors unless metastatic disease is present.

As stated, the epitheleal lining can be discontinuous, and benign and malignant elements can coexist, making biopsies unreliable and, therefore, requiring the pathologic exam of the entire lesion for definitive diagnosis.

We agree that for the most part the classification of microcystic and macrocystic tumors does not have clinical usefulness and that resection is indicated in most instances. To distinguish serous from mucinous lesions would have more clinical and prognostic significance, but frequently this is not possible before resection. I have some questions. How do you advise that these patients be evaluated, because, other than ultrasound, most other studies have limited additional value? Which patient would you observe and how would you follow that patient? What is your opinion in regard to percutaneous aspiration for mucin and glycogen to differentiate serous from mucinous lesions, as suggested in some reports? What are your guidelines for differentiating pseudocyst from cystic neoplasms? In these tumors that have a biology different from that of ductal adenocarcinoma of the pancreas, do you see a value for resection and vascular reconstruction of the superior mesenteric vessels in a case in which it is needed for total resection of the tumor?

DR. W. HARDY HENDREN (Boston, Massachusetts): I would like to ask Dr. Warshaw if the histology of any of these cystic lesions showed either gastric or duodenal mucosa. I have seen several young patients with cystic lesions in the head or body of the pancreas that proved to be duplications. It would seem likely to me that not all such cysts would be symptomatic in childhood. I wonder, therefore, if in examining the wall of any of these cystic lesions, particularly in the younger adults, whether any might have been developmental duplication anomalies that presented in adulthood, and whether some of the tumors may have arisen from either gastric or duodenal cell origin within a pancreatic cystic duplication?

DR. ANDREW WARSHAW (closing discussion): The questions are very much on the mark for this group of tumors. Dr. Hermann, the differential diagnosis from pseudocyst is one of the key problems that we and you and the other discussants have noted. History is certainly important because history is absent in many, but it is also absent in some patients with pseudocysts.

Unfortunately we have not found that CT is reliable for showing septae. When you see them, you see them, but because they still very well may be there, even when not shown by CT, we can't use CT to exclude the diagnosis of pseudocyst.

Fibrosis or scarring around the cyst is not thought to be characteristic of cystic tumors. They are supposed to have nice thin, delicate walls, but it just doesn't turn out to be reliably so. It may be that the absence of epithelium allows the irritating cyst contents to translocate through the wall and cause reaction in the adjacent tissues. The desmoplastic reaction around some cystic tumors can be tremendous and can make the operation quite difficult. Biopsy of the wall does help, but you can't rely on it because of the possibility of sampling an area denuded of epithelium.

It may well be that examining the mucinous contents of mucinous tumors may be as important as the biopsy itself, as suggested by Dr. Howard. There are some reported exceptions, but in our experience the amylase content of these tumors has been low and therefore different from what we observe in a pseudocyst. Cytologic examination often will demonstrate epithelial cells, perhaps malignant appearing, and can be another clue to the fact that the lesion is not a pseudocyst. Elevated levels of CEA and CA-19-9 in the cyst contents have been reported by others. Also staining for mucin, which is not easy on an aspirate, may be helpful. However, because I worry about spreading malignant cells if the contents ooze from the needle hole, we have been hesitant to puncuture the cyst before operation.

The question of arteriography and pancreatography has been raised by several of the discussants. If you believe that angiography is useful in preoperative assessment of pancreatic resections in general, as we do, then I recommend it to you, but not for differential diagnosis of one kind of cystic tumor from another.

Pancreatography, I believe, is mainly useful for those patients in whom you are unsure whether you are dealing with a cystic tumor or with a pseudocyst from chronic pancreatitis. About 50% of our patients had a totally normal pancreatogram, which would certainly argue against chronic pancreatitis with a pseudocyst. Also a cut-off duct in a patient with a cystic tumor indicates cancer in our experience. We saw no communication between the cyst and the pancreatic duct.

Dr. Frey, we have not seen any fistulas into the common bile duct. We have seen reports of tumors that necrosed and communicated with either the pancreatic duct or bile duct.

We have used chemotherapy but not radiation therapy in some of these patients. In an anecdotal way, I can tell you that we have not noted any benefit.

Dr. Howard we have not seen CEA or CA-19-9 elevated in the serum, but as mentioned before, it has been elevated in the cyst contents. We are now looking further at that.

Dr. Pitt, I think your question about lumping *versus* splitting is terribly important. It is true that I have lumped the cystic tumors together for the sake of this report, but I most definitely do not consider them all in the same light. For example, mucinous tumors have high malignant potential and can become aggressive cancers and thus need to be treated as such. Serous tumors have, as far as I can tell, no malignant potential; so that appears to be an all-or-nothing differentiation. The papillary cystic tumors, cystic islet cell tumors, and mucinous ductal ectasia all have substantial malignant potential with rates that have been reported in the 25% to 50% range, but they seem to be somewhat less agressive tumors in most cases.

You also asked about pseudocysts associated with pancreatic cancer and wondered whether we could be throwing a couple of those into the series. I don't think so because our diagnoses were not made on the basis of a solid tumor with an associated cyst but on the basis of an epithelial lining of the cyst itself. Our pathologists are confident also that tumors that were malignant are not serous tumors but mucinous, as previously emphasized.

Dr. Hendren, we are aware of the entity of enteric duplication cysts. We agree that they do cause pancreatitis both in adults and children, as you reported. None of those were included in the current group of patients.

Finally, Dr. Rossi, what is the appropriate workup? I think that for the most part we recognize these tumors now for what they are on the basis of a CT scan and make the decision to operate without much more workup. The extent of evaluation seen in this study is probably not necessary for most patients.

As far as observation *versus* operation, I think it should be exceptional not to operate. In many cases we cannot be sure we are dealing with a benign serous tumor rather than a potentially malignant mucinous one. Some of the serous tumors are symptomatic and warrant operation on that basis. There is a small number of asymptomatic cyst tumors in which there is absolute certainty of diagnosis, perhaps on the base of the sunburst central calcification and angiographic hypervascularity, that might be justifiably and safely observed without resection.

We are perfectly willing to resect the portal vein for pancreatic cancer, and if one of these tumors were stuck to the vessels in that way, we would be willing to attempt appropriate venous excision and reconstruction. We have not yet had to, though.

I conclude with this point. These tumors are often described as having latent or indolent malignant potential. They may go through a premalignant or indolent period of many years, but then something changes. At some point the tumor shifts gears and becomes a highly aggressive cancer equivalent to any other pancreatic cancer. In those patients even resection of the portal vein does not help because the cancer is usually metastatic.

Ileal Pouch–Anal Anastomosis

Reoperation for Pouch-related Complications

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The aim was to assess the value of reoperative surgery for pouch-related complications after ileal pouch–anal anastomosis (IPAA) for chronic ulcerative colitis and familial adenomatous polyposis. Between January 1981 and August 1989, 114 of 982 IPAA patients (12%) seen at the Mayo Clinic had complications directly related to IPAA that required reoperation. Among the 114 patients, the complications prevented initial ileostomy closure in 33 patients (25%), occurred after ileostomy closure in 68 patients (60%), and delayed ileostomy closure in the remaining patients. The salvage procedures performed included anal dilatation under anesthesia for anastomotic strictures, placement of setons and/or fistulotomy for perianal fistulae, unroofing of anastomotic sinuses, simple drainage and antibiotics for perianal abscesses, abdominal exploration with drainage of intra-abdominal abscesses with or without establishment of ileostomy, and complete or partial reconstruction of the reservoir for patients with inadequate emptying. None of the reoperated patients died. Reoperation led to restoration of pouch function in two thirds of patients and, of these, 70% had an excellent clinical outcome. However approximately 20% of the 114 pouches required excision. Excision was common, especially among patients who had pelvic sepsis. Salvage procedures for pouch-specific complications can be done safely and will restore pouch function in two thirds of patients. Complications after reoperation, however, may ultimately lead to loss of the reservoir in one in five patients.

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ILEAL POUCH–ANAL ANASTOMOSIS (IPAA) has increasingly become the operation of choice in patients with chronic ulcerative colitis (CUC) and familial adenomatous polyposis (FAP). Since January 1981, more than 1000 such procedures have been performed at the Mayo Medical Center. With prolonged and ongoing follow-up, several of our patients are presenting or being referred after construction of IPAA outside Mayo Clinic for treatment of specific pouch-related complications. When these complications persist and are recalcitrant to conservative therapy, reoperation may be necessary. We undertook the present study to determine whether reoperation in this subset of patients was safe, to establish how many of these patients ultimately required pouch excision, and to assess functional results after successful salvage operation.

Patients and Methods

Between January 1981 and September 1989, 114 patients underwent reoperation for pouch-related complications after IPAA. Most patients (99) had undergone construction of IPAA at Mayo Medical Center, whereas 15 patients had it established elsewhere. Patients undergoing relaparotomy for small bowel obstruction were not included in this study because we wished to examine only specific pouch-related complications. The medical records of patients were retrospectively reviewed and follow-up information regularly collated by a data clerk or the authors. The following information was documented: age, nature of disease, nature and timing of pouch-related complication, date of IPAA and ileostomy closure where applicable, number of daily and nocturnal bowel movements, need for antidiarrheal medication, and quality of continence. Also recorded were complication-specific symptoms, major indications for and type of reoperation, frequency and type of postoperative complication(s) following "salvage" procedures, and the need for subsequent operations, including pouch excision. Postoperative follow-up was considered complete if information regarding

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pouch function had been obtained in person or *via* telephone interview within the previous 12 months. Patients who underwent pouch excision and/or creation of a permanent Brooke ileostomy were not followed further for the purpose of this report. For those patients with functioning IPAA, the frequency of daily and nocturnal bowel movements was documented, and daytime and nocturnal continence were categorized as either no incontinence, spotting (up to two episodes per week of minor staining of undergarments), or gross (more than two episodes of staining per week or frank incontinence). Postoperative function was considered satisfactory if the patient had no incontinence or spotting and seven or less bowel movements per 24 hours.

Pouch-related complications were divided into four groups: (1) anastomotic stricture; (2) perianal abscess, fistula, or anastomotic sinus; (3) intra-abdominal abscess or fistula; and (4) functional pouch problems. The last group included patients with impaired pouch emptying as well as patients with incontinence. Many patients presented with more than one pouch-related complication, for instance intra-abdominal abscess with anastomotic stricture. In these situations the patients were classified according to the major indication for operation. Data on patients in whom a diagnosis of Crohn's disease was eventually established clinically or on the basis of subsequent histology were analyzed separately.

Statistical Analysis

Means are listed ± standard deviation. Comparisons of proportions were made with chi square tests and comparisons of continuous variables made with rank-sum tests. The distribution or ordinal values, such as incontinence, were compared in two or more groups using rank-sum tests. The Bonferroni method was used to adjust p values for multiple comparisons. The probability of avoiding pouch excision was estimated as a function of time using the Kaplan–Meier method. P values less than 0.05 were considered statistically significant.

Patient Population

Among the 114 patients (56 female and 58 male) who had pouch-related complications, the mean age was 30 years (range, 10 to 64 years). Diagnoses were as follows: chronic ulcerative colitis (CUC), 90 patients (79%); familial adenomatous polyposis (FAP), 7 patients (6%); Crohn's disease initially diagnosed as CUC or indeterminant colitis, 16 patients (14%); and chronic constipation, 1 patient (1%). Eighty-two per cent of patients had J-shaped reservoirs, 9% had S-shaped reservoirs, and 9% had other types of pouches. All but four patients had a diverting ileostomy established at the time of IPAA, and 36% of patients had a diverting ileostomy still in place before reoperation for complications. Pouch-related complications occurred before ileostomy closure in 43 patients (38%) and prevented ileostomy closure in 33 of these patients. Ileal pouch–anal anastomosis-related complications were as follows: anastomotic stricture, 42 patients; perianal abscess/fistula/sinus, 30 patients; intra-abdominal abscess/fistula, 29 patients; and unsatisfactory pouch function, 13 patients. All patients with perianal or intra-abdominal abscess or fistula had symptoms; however 29% of patients with anatomically important strictures were asymptomatic.

Results

No deaths were associated with reoperative surgery. Postoperative complications after operation for pouch-related complications developed in 70 patients (61%) overall. All but one of these patients underwent one or more subsequent operations (range, 1 to 13 operations). Patients were followed for a mean of 37 ± 20 months after operation (range, 1 to 98 months). At follow-up, 22 patients had their pouches excised, 15 patients had ileostomies with intact pouches, and 77 patients had functioning IPAAs. Of these 77 patients, 54 (70%) had satisfactory functional results (seven or less bowel movements per day, no incontinence, or mild fecal spotting two or less times per week).

Anastomotic Stricture

Presentation. Such strictures occurred in patients with CUC and in patients with FAP. Strictures were most frequently diagnosed after ileostomy closure. Patients presented most frequently with one or more symptoms of outlet obstruction (*i.e.*, straining; 36%), diarrhea (50%), anal pain (12%), or obstructive abdominal pain (12%).

Treatment and postoperative complications. Initially all patients were treated by dilatation under anesthesia using Hegar dilators. Recurrent strictures and other complications occurred in 25 patients (60%) (Table 1). All of these patients underwent further operation. Recurrent strictures were dilated at least once (mean ± SD, 1.8 ± 1.6; range, one to seven times). Ultimately 6 of the 42 patients had their pouches excised due to recurrent stenosis (n = 3), diarrhea (n = 1), or persistent perianal fistulae (n = 2). Pouch excision was performed 69 ± 39 months after reoperation for pouch-related complications. In patients with diverting ileostomy at the time of operation for pouch-related complications, ileostomy was closed a mean of 24 ± 37 months later.

Functional results. Patients in this group were followed for a mean 40 ± 19 months after the initial dilatation. One patient was lost to follow-up. Seven patients still had a diverting ileostomy at follow-up. In those patients with functioning IPAAs at follow-up, 11 patients had recurrent

TABLE 1. *Procedures Used to Correct Pouch-specific Problems and Their Postoperative Complications*

	No. of Patients (%)			
Category	Anastomatic Stricture (n = 42)	Perianal Fistula/Abscess (n = 30)	Intra-abdom. Fistula/Abscess (n = 29)	Unsatisfactory Function (n = 13)
Ileostomy at presentation	13 (31)	10 (33)	15 (52)	3 (23)
Frequent Procedures Performed				
Dilatation of associated stricture	42 (100)	9 (30)		2 (15)
Fistulotomy/excision of fistula tract		17 (57)	4 (14)	
Primary closure of fistula		3 (10)	3 (10)	
Drainage of abscess		5 (17)	18 (62)	
Diverting ileostomy		3 (10)	6 (21)	
Redo IPAA			5 (17)	4 (31)
Divide pouch septum				4 (31)
Sorten or excise efferent limb				2 (16)
Convert to different type pouch				3 (10)
Postoperative Complications	25 (60)	23 (77)	18 (62)	4 (31)
Recurrent stricture	22 (52)	6 (2)		
Perianal fistula	2 (5)	16 (53)		
Perianal abscess	1 (2)	5 (17)		
Intra-abdominal fistula			5 (17)	1 (8)
Intra-abdominal abscess			9 (31)	1 (8)
Other				2 (16)
More than 1 operation for pouch-related complications	25 (60)	22 (73)	17 (59)	5 (38)

IPAA, ileal pouch–anal anastomosis.

stricture requiring intermittent dilatation and 52% of patients were taking anti-diarrheal or bulk-forming medication, compared to 36% before operation. After reoperation for stricture, daytime and nighttime stool frequency decreased from 14 ± 11 stools per day before operation to 7 ± 3 stools per day and from 2 ± 1 to 1 ± 1 stools per night (Fig. 1). Continence also improved (Fig. 2). Satisfactory functional results were achieved in 69% of patients with functioning IPAAs at the time of follow-up (Table 2).

Perinanal Abscess/Fistula/Sinus

Presentation. This complication was not observed in polyposis patients. Frequent presenting symptoms included perianal abscess or purulent drainage in 24 patients (80%), diarrhea in 11 patients (37%), fever in 5 patients (17%), anal pain in 6 patients (20%), an associated anastomotic stricture in 5 patients (17%), or a combination of these.

Treatment and postoperative complications. The procedures performed are listed in Table 1. The most common were local perianal operations. Postoperative complications occurred in 23 patients (77%), and 22 of these underwent further operations, which included fistulotomy (10 patients), dilatation of anastomotic stricture (5 patients), primary fistula closure (2 patients), and diverting ileostomy (2 patients). Six of these patients required additional operations, with a mean 3 ± 5 procedures performed per patient. Five of thirty patients (17%) subsequently underwent pouch excision a mean of 59 months after the initial operation for pouch-related complications.

Functional results. At follow-up, 10 of 30 patients (including patients with pouch excision) had diverting ileostomies. The mean postoperative follow-up after operation for pouch-related complications was 36 ± 19 months; one patient was lost to follow-up. Fourteen of thirty patients (47%) were taking antidiarrheal or bulk-forming medications compared to 43% patients taking them before operation. Compared to preoperative values, postoperative stool frequency decreased from 11 ± 5 to

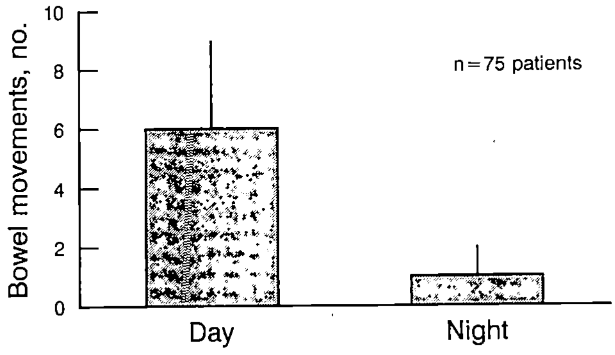

FIG. 1. Mean frequency ± SD of stooling in patients after reoperation for pouch-related complications among subjects with the ileal pouch–anal anastomosis.

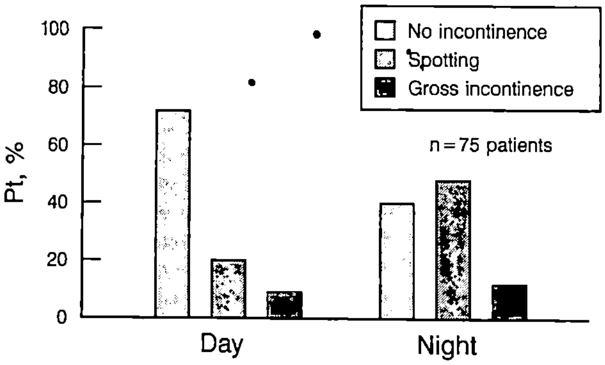

FIG. 2. Degree of fecal continence in patients after reoperation for pouch-related complications among subjects with the ileal pouch–anal anastomosis.

6 ± 2 stools per day and from 4 ± 4 to 1 ± 1 stools per night (Fig. 1). Continence improved after operation (Fig. 2). Satisfactory functional results were achieved in 70% of patients with a functioning IPAA at the time of follow-up (Table 2).

Intra-abdominal Abscess/Fistula

Presentation. There were no polyposis patients in this group. Major symptoms included fever (76%), local or generalized peritonitis (45%), abdominal pain (38%), and diarrhea (35%). Fifty-two per cent of patients had a diverting ileostomy in place before operation for this complication.

Treatment and postoperative complications. The surgical procedures performed are listed in Table 1. The most common was drainage of the intra-abdominal abscess. Complications developed in 18 patients (62%) after these procedures, including, alone or in combination, recurrent intra-abdominal abscess(es) (31%), intra-abdominal fistula (53%), or stricture (20%). Fifty-nine per cent of the patients in this group required further operations. Ten patients required abscess drainage, primary closure of pouch fistula (2 patients), and reconstruction of IPAA with diverting ileostomy (1 patient). Ten pouches (34%) were eventually excised a mean 47 ± 33 months after operation for pouch-related complications.

Functional results. At follow-up, 17 patients (including those with pouch excision) had a diverting ileostomy. Twenty-one per cent of patients were taking antidiarrheal or bulk-forming medication compared to 28% taking these medication before operation. Compared to preoperative values, postoperative stool frequency decreased from 15 ± 12 to 5 ± 2 stools per day and from 2 ± 0 to 1 ± 1 stools per night (Fig. 1). Continence improved after operation (Fig. 2). Eighty-three per cent of patients with a functioning IPAA at the time of follow-up had satisfactory pouch function (Table 2).

Unsatisfactory Function

Presentation. This heterogeneous group of 13 patients included both patients with inflammatory bowel disease (n = 11) and FAP (n = 2). Three of these patients had a previous S pouch constructed, seven patients had a J pouch, and the other three patients had other types of pouch–anal anastomosis. Prerevision functional problems included long efferent limb in 3 S-pouch patients, incontinence related to too small or too large a reservoir size or intra-abdominal pouch location in 3 patients, obstruction secondary to a J-pouch septum in 4 patients, outlet obstruction due to mucosal prolapse in 1 patient, small capacity pouch in 1 patient, and recurrent pouchitis due to poor pouch emptying in another patient.

Treatment, postoperative complications, and results. The procedures performed and postoperative complications are listed in Table 1. The most common procedure was revision of the pouch. Compared to preoperative values, postoperative stool frequency decreased from 14 ± 7 to 8 ± 6 stools per day and from 3 ± 2 to 2 ± 2 stools per night (Fig. 1). Postoperative continence is shown in Figure 2. Satisfactory functional results were achieved in 60% of patients who had a functioning IPAA at the time of follow-up (Table 2).

TABLE 2. *Postoperative Pouch Function After Salvage Operation for Pouch-specific Problems*

	No. of Patients (%)			
	Anastomotic Stricture	Perianal Fistula/Abscess	Intra-abdom. Fistula/Abscess	Unsatisfactory Function
Ileostomy closed				
Anal-pouch function satisfactory	23 (56)	13 (45)	10 (35)	6 (46)
Anal-pouch function poor	11 (27)	6 (21)	2 (7)	4 (31)
Ileostomy present				
Pouch *in situ*	1 (2)	5 (17)	7 (24)	2 (15)
Pouch excised	6 (15)	5 (17)	10 (34)	1 (8)
Total	41	29	29	13

Mean ± SD follow-up, 37 ± 20 months.

Crohn's Disease

Of these 16 patients, 4 had an ileostomy before operation for IPAA-related complications and another 4 patients experienced complications before closure of ileostomy. All patients within this group presented with diarrhea. A perianal abscess or draining fistula was present in 44%, stricture in 31%, incontinence in 19%, and anal pain in 19% of patients. Major indications for operation were stricture in 56% of patients, fistula/sinus in 56%, and pelvic abscess in 19%. The fistulae consisted of 2 perianal fistulae, 1 rectovaginal fistula, and 5 anastomotic sinuses. Procedures performed included dilatation of a stricture in 44% of patients, fistulotomy in 31%, and abscess drainage in 13%. Fourteen of sixteen patients (80%) had complications after these procedures, including anastomotic stricture in 25%, abscess in 25%, and fistula in 31%. All of these patients underwent further operations. Patients were followed for a mean of 62 ± 49 months after surgery for pouch-related complications. Fifty-six per cent of patients had diverting ileostomy at follow-up, including four patients who ultimately required pouch excision.

Intergroup Comparative Analysis

Overall length of follow-up, degree of incontinence, and the frequency of bowel movements after operation did not differ significantly between groups. The proportion of patients older than 25 years was greater (71%) in the groups with anastomotic stricture and unsatisfactory pouch function (85%) than in the groups with perianal abscess/fistula (40%) and intra-abdominal abscess/fistula (55%). No FAP patients were observed to have septic complications (perianal or intra-abdominal). The presence or absence of an ileostomy at presentation, sex, time of diagnosis of the complication with respect to ileostomy closure, and rate of subsequent operation and pouch excision were not appreciably different between complication groups. Sixty-nine per cent of patients requiring more than one operation for pouch-related complications ultimately had the pouch excised compared to 14% of patients who had undergone only one operation for pouch-related complications. Figure 3 illustrates the probability of remaining free of pouch excision over time in all patients. Patients with intra-abdominal abscess/fistula were less likely to avoid pouch excision over time (Fig. 4).

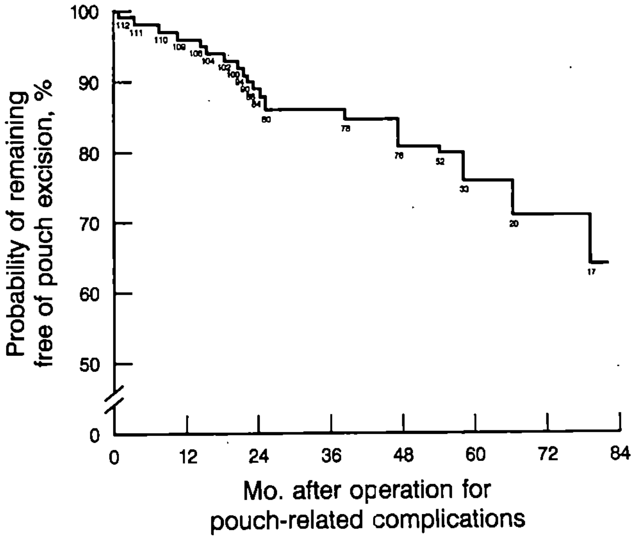

FIG. 3. Probability of pouch excision against time among all patients with pouch-related complications requiring operation after ileal pouch–anal anastomosis.

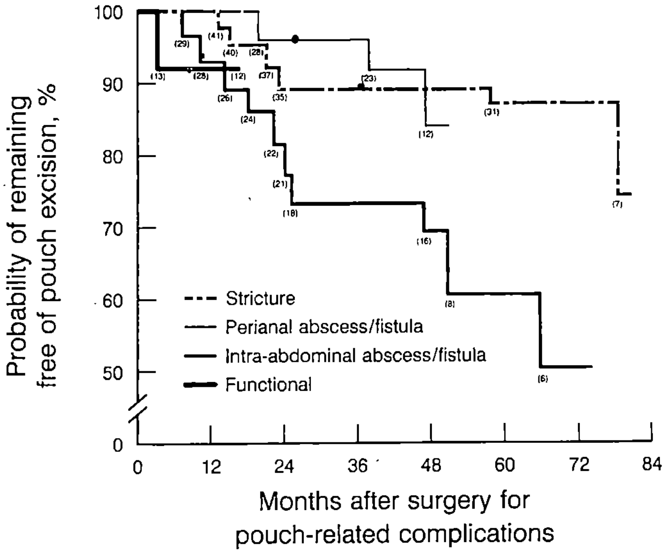

FIG. 4. Probability of pouch excision against time among groups of patients with pouch-related complications requiring reoperation after ileal pouch–anal anastomosis.

Discussion

With the increasing use of IPAA and prolonged follow-up, more reports of complications following this procedure are appearing in the literature. These complications, which range from relatively benign IPAA strictures to life-threatening intra-abdominal abscesses, may in some instances be corrected by reoperation. Our results would indicate that such salvage operations can be done safely and that the risk of further complications and pouch excision is elevated but that satisfactory neorectal function can be restored in 70% of patients with functioning pouches.

The risk of stricture has been reported to be 8% to 14% following IPAA.[1] In the Lahey Clinic series, all IPAA strictures were noted before ileostomy closure, whereas in the present series, 64% of strictures were noted after ileostomy closure, a mean of 8.5 ± 10 months after IPAA.[1] Recurrent or unrecognized IPAA stricture may impair pouch emptying and favors recalcitrant pouchitis, and, indeed, the incidence of pouchitis decreases after treatment of strictures.[2] Shoetz[1] reported that 7.7% of patients required an ileostomy due to a persistent stricture compared to 17% of patients with an ileostomy at follow-up in our series. Repeated dilatation of strictures or repeated procedures such as curettage or fistulotomy may result in fibrosis and incontinence. Emblem et al.[3] showed an inverse correlation between anal canal resting pressure and the amount of sphincter fibrosis. Some authors believe that preoperative anal sphincter spasm in CUC patients may be related to longstanding diarrhea or inflammation and that extension of this inflammatory process into the muscularis may cause pouch stasis and inflammation.[2] Strictures also are more common in patients with CUC than in those with FAP.

Ileal pouch–anal anastomosis fistulae may result from drainage of an abscess through the IPAA or result from anastomotic ischemia and/or dehiscence. In patients with anastomotic complications that occur before ileostomy closure, several months delay in closure of the stoma, with a pouchogram before re-establishment of intestinal continuity, may be warranted before operative correction of this problem is attempted. In our series such complications resulted in a delay in ileostomy closure in 42% of patients. In patients in whom the ileostomy had been closed or in those with symptomatic fistulae, sinus tracts, or abscesses before ileostomy closure, a variety of procedures may be performed. These include fistulotomy, curettage of the fistula, placement of a seton, advancement flap repair, and abscess drainage, all with or without diversion.[4] In 15 of 19 patients (79%) in a recent series, perianal anastomotic complications were diagnosed before ileostomy closure either by pouchogram or examination.[4] Thirty-nine operations were performed in 19 patients, with three pouches (16%) ultimately requiring excision. This is comparable to the 17% rate of pouch excision after surgery for anastomotic abscess and fistula in this study. In contrast to the present study, all of Schoetz's patients with post-IPAA fistula required diverting ileostomy, as compared to 30% of patients in this series.[1]

Rates of pelvic sepsis after IPAA have been reported from 0% to 25%.[5–7] At our institution early reports of an 11% rate of pelvic sepsis decreased to 5% as experience with this technique increased.[5,6] The decrease in pelvic sepsis rate over time also may be due to the use of a shorter rectal cuff. Presacral abscesses may arise from intraoperative contamination of the presacral space or from partial IPAA separation. One study also has demonstrated an increased rate of pelvic sepsis in patients with incompletely diverting ileostomies as compared to patients with complete diversion.[5] If a CT scan of the pelvis reveals no discrete abscess, intravenous antibiotics alone may be therapeutic in one third of these patients.[6] If a discrete fluid collection is identified on CT scan, CT-guided or operative drainage may be attempted. In our previous report, 17 of 30 patients with pelvic sepsis after IPAA required laparotomy, as compared to only one of six patients in another report.[1,8]

Comparison of postoperative results in patients with CUC and FAP has shown a 6% rate of pelvic sepsis requiring reoperation in CUC patients, compared to 0% in patients with FAP.[2] Similarly the rate of pouch excision in CUC and FAP patients was 3.2% and 0%, respectively.[2] This is in agreement with the fact that no FAP patients were among the perianal abscess/fistula or intra-abdominal abscess groups. Correspondingly functional results in FAP patients also have been shown to be superior to those in CUC patients.[2] Pelvic sepsis may result in a frozen pelvis with a nondistensible reservoir and subsequent poor functional results. Some authors, therefore, believe that subtotal colectomy and ileostomy before IPAA will lead to resolution of pelvic inflammation in CUC patients and result in a more resilient and pliable reservoir and improved pouch function after operation. The rate of pelvic septic complications was not lower in patients with previous colectomy, which correlates with a previous report from this institution.[8] A review of patients with indeterminate colitis has shown that the rate of reoperation for sepsis was 4% in CUC patients compared to 18% for patients with indeterminant colitis.[9]

Functional results after laparotomy for intra-abdominal abscess in this report are slightly worse than reported previously (8 ± 6 daily bowel movements *versus* 6 per day).[1] In the latter report, which included patients that required laparotomy for their sepsis and those that did not, 29% of patients had their ileostomies closed at follow-up compared to 41% in our patients; similarly 41% of patients in the former study required pouch excision compared to 34% in the present series.[1] Scott et al.[8] found that pelvic sepsis did not influence continence. In the present study, the mean time of pouch excision following IPAA for all groups, except that with functional problems, was more than 47 months after operation.

In the category of patients with functional problems, 23% of patients had impaired emptying of an S-pouch secondary to a long efferent limb. Long efferent limbs previously were associated with a higher rate of postoperative complications.[10] In these patients the efferent limb was shortened in one, excised in another, and the S pouch converted to a J pouch in a third. Pouch mobilization with shortening of the efferent limb has been used successfully in the past to achieve improved functional results.[11,12] In Schoetz's report,[1] this problem was corrected in three patients by transanal division of the septum between the pouch and the efferent limb using a linear stapler, and no ileostomy was necessary.

In choosing only patients requiring operation for inclusion into our study, we necessarily excluded all those patients with complications that were treated by intravenous antibiotics, delay in ileostomy closure, or dilatation without anesthesia. For this reason functional results following pouch-related complications in IPAA patients may be less favorable than expected. As experience is gained in dealing with these complications, it has become apparent that these patients are at significant risk of requiring subsequent pouch excision (19%). In those patients without ileostomy who retain their reservoir, however, satisfactory function may be achieved in 70% of patients.

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DISCUSSION

DR. STANLEY M. GOLDBERG (Minneapolis, Minnesota): First I would like to thank Dr. Galandiuk and her associates from the Mayo Clinic for the privilege of reviewing their manuscript and permitting me to comment on their paper.

I would like to compliment them on their excellent results following reoperative surgery.

As Dr. Galandiuk, stated, there were no deaths in this group, and 54 of the 114 patients, or 48%, had a satisfactory functional result.

As pertains to the rate of complications *versus* operative experience, your institution previously reported a pelvic sepsis rate that has decreased from 11% to 5% as experience with this operative technique increased.

You do not state if other complications have decreased, such as stricture, fistula, and functional result. The work from our institution suggests that the incidence of these complications has decreased with experience. I would appreciate your comments on this point.

Moving on to the problem of stricture formation, I was curious to know whether there was any relationship between stricture formation and pouch type. We have found that the J pouch will not always reach deep into the pelvis without putting tension on the anastomosis. I am curious to know what factors contribute to stricture formation. Could the end-to-side anastomosis of the J pouch contribute to stricture formation because of the anastomotic ischemia?

In reviewing your data, almost 50%, or 49% to be exact, of the pouch excisions resulted from intraabdominal abscess. No patient with familial adenomatous polyposis was in this group. All of these patients had inflammatory bowel disease. This prompts a question. Should we continue to advise patients who are chronically ill and immunosuppressed to undergo an ileal pouch–anal anastomosis at the time of the initial colectomy?

Your institution has shown that incomplete diversion of the ileostomy results in a higher rate of pelvic sepsis. Should we perform a completely diverting ileostomy, such as a split ileostomy, for this high-risk, immunosuppressed group of patients?

I realize that pouchitis is an ill-defined entity. In our series, which was recently reported by Dr. Wexner, the incidence of pouchitis approached 50% at 5 years. We have had to excise several pouches because of recurrent pouchitis. Have there been any pouch excisions at your institution because of recurrent pouchitis?

The problem of differentiating Crohn's disease from mucosal ulcerative colitis can be difficult. Of your 16 patients with Crohn's disease, in retrospect, was there any indication at the time of the initial operation that would have given you a hint and suggested the possibility of this diagnosis?

If faced with these findings today, would you consider an ileal-rectal anastomosis rather than a pouch–anal anastomosis?

There are a number of alternative techniques that have been advocated to improve functional results. Do you think that a nonmucosectomy, double-staple technique, as popularized by Professor David Johnston in Leeds, would decrease or increase the complications associated with ileal pouch–anal anastomosis?

I want to close by thanking you and your associates for drawing our attention on the complications and their consequences associated with the ileal pouch–anal anastomosis. This serves to caution us in the overzealous application of this procedure to patients with inflammatory bowel disease and familial adenomatous polyposis.

DR. JOSEF FISCHER (Cincinnati, Ohio): First I would like to congratulate Dr. Galandiuk for an excellent presentation of a complicated group of patients and the entire Mayo Clinic group for bringing us not only the good side but the downside of a new operation.

I just have a few questions. First is it routine, before closing the pouch, for the patients to have the pouchogram?

Second I would like to confine my remarks to that small group with unsatisfactory 'pouch function' because I suspect if we understood that group of patients, perhaps we would do a lot better with the entire group.

How big should a pouch be? What should its capacity be? I know you have done some pressure–volume relationships. Have you achieved some understanding or some bias as to how large the pouch should be and what its capacity should be?

The other aspect of the unsatisfactory functional pouch is the length, at least in the S pouch, and perhaps in some patients with the J pouch, of the outlet sleeve, we think this should be very short term. Do you have some bias or some opinion about what the proper length of the outlet should be?

There is a small group of patients in our series who, despite the fact that the length of the outlet spout is 1 cm at the time of surgery, inexplicably come back with an outlet that seems to grow to be about 4 or 5 cm, and in those patients, 4 in number, there has been 'unsatisfactory' pouch function.

When this segment has been revised transanally and the outlet spout has been shortened without changing the pouch, the pouch function becomes satisfactory once again.

If there is a stricture at the pouch–anal anastomosis, the stricture is the result of ischemia as I think you and I, and I believe Stan Goldberg suspect, then I would advocate perhaps greater emphasis on a transanal approach for revision of some of the outlet dysfunction. It might be that some parasitic blood supply from the sidewalls of the pelvis might help prevent the recurrence of the ischemia that may occur if the pouch were completely mobilized from above, and I wonder what are your thoughts and your experience about this.

DR. MALCOLM C. VEIDENHEIMER, (Burlington, Massachusetts): I would like to thank the authors for sending me a copy of their manuscript. It is much more detailed than what could be presented today and is an important contribution. When I joined the staff of the Lahey Clinic some years ago, I was told a story about Dr. Lahey experiencing a gas explosion in the operating room and promptly making the facts of this know to the American surgical world.

When one has an image that has been shined furiously by past reputation, it cannot be tarnished by telling the downside of a story such as has been told today by the Mayo Clinic people. It seems appropriate that our Mayo colleagues, who have the world's largest experience with mucosal proctectomy, should share with us some of the problems they have had in the management of their patients.

This group of 114 patients requiring surgical treatment for pouch-related complications represents 12% of their total of 982 patients. The authors report valiant efforts to salvage pouch function, and although a little more than 50% of their series ended with poor function, this was only after continued efforts by Mayo surgeons over an average time frame of 4 years, and with up to 14 different operations attempted to salvage an individual pouch. This was surely worthwhile for those in whom the pouch has been salvaged.

In our experience, which is much less than theirs, our patients have an average of five bowel movements each day. We have a small incidence of incontinence, and when one attends support group meetings and listens to these patients talk about their life without an ileostomy, all the effort has proved worthwhile both for them and for us.

I do have some questions for the authors. Do you have an explanation for what seems to be a higher incidence of reoperation for pouch problems? As Dr. Stanley Goldberg has asked, have you been able to relate their complications to tension at the ileoanal anastomosis? Our British colleagues have studied the pouch for evidence of ischemia. Have Mayo surgeons performed any such studies?

Five per cent of our pouches are S pouches. They were pouches performed in our early experience and probably represent the early learning curve in our practice. However, as we have reviewed our pouch complications, a large percentage have occurred in S pouch patients. In the Mayo paper 18% of their patients had some other kind of pouch than the J pouch. Do you think that their problems have represented a skew into that group of pouch patients compared to those with J pouches?

Is there evidence that there has been a lessening of pouch complications as experience increases?

This is, of course, a fine paper and very useful to all of us. I'm grateful that our Mayo Clinic colleagues have the courage to tell us about some of their downside results.

DR. GARDNER SMITH (Baltimore, Maryland): I would like to join the chorus of those who are thanking Dr. Galandiuk and her colleagues for adding yet another marvelous bit of information to this tremendous experience that they have. I simply want to ask about a potential complication, wondering if they have encountered it and if not, why not. This has to do with patients who have had pouches excised or, particularly, those who have had the afferent limb revised in some way. Have there been any problems with impotence in men, and if not, are there any tricks that you have to avoid that problem?

DR. ROGER R. DOZOIS (Closing discussion): One should keep in mind that this group of patients represents only the pouch-related complications and only about 10% of our entire experience.

I would also make the point that this procedure, although it has become the most favored procedure in most patients with ulcerative colitis, is not an operation for all patients with ulcerative colitis and there is still a place and a role for the other procedures.

Dr. Goldberg asked about the complications other than sepsis and whether these have decreased over time. My suspicion is that they have also decreased over time, but we have not thus far analyzed this carefully, and therefore, I cannot answer more specifically.

The formation of stricture is, I am sure, due to multiple factors. Certainly ischemia and tension may be contributing factors, and if there is a problem with having the pouch reach the anal area, one should attempt to mobilize the mesentery further or, if this is not possible, for example, in obese patients, use alternative designs of reservoirs like the S pouch or the W-shaped pouch, which may reach better.

One should tailor the type of pouch that is used according to the anatomy of the patients, but I must say that in most patients, we find that the J-shaped pouch will reach the anal area without difficulties if the mesentery is mobilized appropriately.

There is another cause, I think, of anal stricture and that is partial disruption of the anastomosis in the immediate postoperative period with secondary healing and stenosis.

And this again may relate to tension. It may also relate to local infection in that area of the anastomosis, and if this can be diagnosed early, one should drain this site with the hope of avoiding development of a stricture.

Should we use a completely diverting ileostomy instead of a loop type of ileostomy? Our hope is that the loop ileostomy, if it is properly performed, will completely divert the fecal stream away from the pouch. If the spout is not adequate, one may have incomplete diversion and, in turn, favor infection at the level of the pouch.

We also always urge the patient to empty their ileostomy appliance regularly so that is does not overflow into the distal limb of the loop ileostomy.

As far as pouch excision due to pouchitis is concerned, we have not had to do this. We have had patients who were initially thought to have pouchitis and continued to have increasingly severe symptoms and eventually had their pouches removed to find that, in fact, they had Crohn's disease. And this leads me to the other question of Dr. Goldberg's, and that is were there any indications at the time of the original surgery that might have given us a hint as to whether we were, in fact, dealing with Crohn's disease?

Well, to be honest, I would have to say no, although we have found through the years that patients who have had a previous perianal abscess or a fistula and even though the pathologist may tell us at the time of surgery that we are dealing with ulcerative colitis, in fact, will often turn out to have Crohn's disease; one should therefore, be very cautious about doing an ileal pouch–anal anastomosis when there is a previous history of perianal fistula or abscess or both.

If we are uncertain about the diagnosis at the time of surgery, we have several choices, of course. We can do a regular type of ileostomy, but I do think, like Dr. Goldberg suggested, that if the rectum is not severely diseased and if the ability of the rectum to distend is still present, one should probably do an ileorectal anastomosis and the patient will have an opportunity to see what will develop later on as far as further disease. This would also give more chance for the patohölgist to examine the tissue.

As far as the nonmucosectomy technique, I am not certain that we can answer this question, Dr. Goldberg, because we have not used this technique. Certainly the aim is to reduce the problems with incontinence, especially at night, a minor type of incontinence, and the proponents of this procedure have reported better continence results. However we are concerned that leaving behind this short segment of mucosa may cause other types of complications. These would include recurrence of the disease at the level of the anastomosis or the future development of cancer.

We hope both of these problems would be unusual, but we don't have enough follow-up data to determine whether leaving behind this segment of mucosa will result in these complications. Certainly in the literature there is evidence that this area does contain a glandular epithelium because patients with previous ulcerative colitis have developed dysplasia and one patient has developed cancer in that short segment. Another group from Scandinavia has reported the development of adenomatous polyps in that short transitional zone mucosa, so that area does again contain glandular epithelium.

Dr. Fischer asked if we should do a routine pouchogram before closure of the ileostomy. I would have to say that we usually do a pouchogram and a proctoscopic examination before closure of the ileostomy.

What sort of pouch size would be ideal to help prevent unsatisfactory function? Our practice has been to use primarily the J-shaped reservoir using 15- to 18-cm limbs of the distal ileum. With this type of approach, we have found that at 18 months the reservoir capacity of the J-shaped pouch is about 380 cm of water, which is no different from that of the normal rectum. Again there are other factors that may favor or interfere with emptying other than the pouch capacity, which is only one factor.

The length of the outlet is an interesting question, and I am glad that Dr. Fischer brought that up. Of course we don't, in general, do S-shaped reservoids, although we have done some and several groups, including the group from Minneapolis, have shown clearly if you make that limb no longer than 2 cm you will prevent a lot of the pouch emptying problems. However we have noticed that some of these efferent limbs will elongate over a period of time. This may have something to do with the fact that we have reserved the use of the S-shaped pouch for patients who had difficult anatomy and where we could not reach the dentate line area with the J-shaped pouch.

However there may be some other reasons. In fact, Mr. Nichols of England has recently published a paper in which he has shown that even if you remove the efferent limb, two of five patients continued to have emptying problems and they needed to catheterize themselves, so the efferent limbs, as it pertains to the S-shaped reservoir, is not the only factor that may interfere with emptying, and this needs to be studied further.

We have used both the transanal approach and abdominal approach to repair stricture problems, and I can tell you from experience that by and large we get better control of the situation and better results if a transabdominal approach is used.

Dr. Veidenheimer asked a question pertaining to tension, and I think I have already responded to this.

We have not studied ischemia, as the British authors have, but I have to say in response to this that to me ischemia is unlikely to be the answer because the kind of problems we see with ulcerative colitis, intervals of pouchitis pertaining to ischemia, we do not see with polyposis in which the same technique is used and other similar factors are present.

We agree with you, Dr. Veidenheimer, that because we use primarily the J-shaped reservoir, our data are skewed that way.

Finally, Dr. Smith, impotence in male patients has been seen in less than 1%. We try to avoid the area of the promontory by leaving behind the retrorectal fat, so we don't cause any problem with retrograde evacuation and the dissection of the rectum further distally if carried out by staying very close to the rectal wall.

The Role of Prostanoids in the Production of Acute Acalculous Cholecystitis by Platelet-activating Factor

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Gallbladder tissue from patients with acute acalculous cholecystitis contains increased amounts of prostanoids when compared to normal gallbladder tissue. Platelet-activating factor (PAF) is a potent stimulus of eicosanoid formation. It has been implicated as a mediator of acute inflammatory processes and systemic responses to shock. In this study the role of PAF in acute acalculous cholecystitis was evaluated. Anesthetized cats underwent gallbladder perfusion with a physiologic buffer solution containing [^{14}C] polyethylene glycol as a nonabsorbable tracer to quantitate mucosal water absorption. Platelet-activating factor was infused into the hepatic artery for 2 hours. Control experiments were performed when vehicle alone was infused. Experiments also were performed when indomethacin was administered intravenously and when indomethacin and PAF were administered. Gallbladder mucosal absorption/secretion and perfusate and tissue prostaglandin E (PGE) and 6 keto prostaglandin $F_{1\alpha}$ (6-keto $PGF_{1\alpha}$) levels were evaluated. Gallbladder inflammation was evaluated by β-glucuronidase and myeloperoxidase tissue concentrations and by a histologic scoring system. Platelet-activating factor eliminated gallbladder absorption and produced net fluid secretion associated with dose-related increases in perfusate PGE concentrations and gallbladder tissue PGE and 6 keto $PGF_{1\alpha}$ levels when compared to control values. Platelet-activating factor produced significant inflammation in the gallbladder with increases in the histologic score of inflammation and tissue lysosomal enzyme activities. Indomethacin significantly decreased the fluid secretion, prostanoid levels, and inflammation produced by PAF. The results suggest that PAF may induce acute gallbladder inflammation associated with systemic stress through a prostanoid-mediated mechanism.

PLATELET-ACTIVATING FACTOR (PAF) is a putative mediator of shock and inflammation.[1,2] It is an autacoid released by a wide variety of cells including basophils, eosinophils, neutrophils, macrophages, monocytes, mast cells, vascular endothelial cells, kidney, and smooth muscle.[2,3] Platelet-activating factor administration produces systemic hypotension, increased vascular permeability, and neutrophil aggregation and degranulation, suggesting that it is involved in producing inflammatory processes and shock.[4–6]

Platelet-activating factor has been proposed as an important endogenous mediator of gastrointestinal damage and ulceration associated with shock.[7,8] In the present study, it was intended to determine if PAF produced inflammatory changes in the gallbladder. Acute acalculous cholecystitis is an important disease process associated with shock.[9] In humans acutely inflamed gallbladders from patients with acute acalculous cholecystitis produce increased eicosanoids compared to normal gallbladders.[10] As eicosanoids mediate the activity of PAF in other systems,[11,12] it was intended to determine if eicosanoids played a role in any gallbladder changes produced by PAF.

Methods

Twenty-four cats, weighing 2 to 3 kg each, were fasted for 24 hours but allowed water. Before the operations, the cats were sedated with acepromazine maleate (4 mg/kg). The animals, anesthetized with pentobarbital at 25 mg/kg, underwent endotracheal intubation and were artificially ventilated with a positive-pressure respirator, using an inspired oxygen content of 40%, tidal volume of 15 mL/kg, at a rate of 15 breaths per minute. Throughout the 4-hour experiments, supplemental pentobarbital anesthesia was administered as indicated. The experiments performed were evaluated and approved by the Institutional Animal Care Committee of St. Louis University Hospital.

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Arterial pressure was monitored using a PE90 catheter inserted 6 cm into the femoral artery, with a calibrated strain gauge (Stratham, Oxnard, CA). Body temperature was monitored with a rectal thermistor and throughout the experiments the animals were maintained in a normothermic state, using a water-filled heating–cooling blanket. Through a PE90 catheter inserted 6 cm into the femoral vein, the animals received intravenously 0.5 mL/kg/hour 0.15 mol/L (molar) NaCl solution.

Through an abdominal incision, a metal clip was placed occluding the cystic duct, preserving the cystic artery. A PE90 catheter was placed through the gastroduodenal artery into the hepatic artery and infused with 0.15 mol/L NaCl solution into the hepatic artery at a rate of 0.5 mL/kg/hour.

The gallbladder was intubated through the fundus with two 6 French olive-tipped catheters, with sutures used to prevent leakage around the catheters. The inflow catheter was placed toward the cystic duct and the outflow catheter was positioned at the fundus. The gallbladder was irrigated with 0.15 mol/L NaCl solution until clear.

Perfusion was performed with a constant infusion pump at 10 mL/hour. The infusion pressure was maintained at 2 to 7 cm constantly with a water manometer in the infusion system. A nonabsorbable tracer, [^{14}C] polyethylene glycol ([^{14}C] PEG), was added to all the perfusates at a concentration of 2 μ Ci/100 mL of perfusate. The fluid transport by the gallbladder was calculated from the perfusion rate and the concentration change in the marker as it passed through the gallbladder according to the standard formula described previously.[13]

$$\text{Net water absorption} = \text{Qin} - \frac{\text{Qin} \times \text{Cin}}{\text{Cout}},$$

where Q = volume and C = concentration of [^{14}C] PEG.

Normal or inflamed gallbladder mucosa does not absorb PEG[14] and bile does not enter the feline gallbladder through aberrant biliary radicles affecting the results.[15]

After cannulation and irrigation of the gallbladder, perfusion for 1 hour with 0.15 mol/L NaCl solution was performed to stabilize the system. Subsequently the gallbladders were perfused for 3 hours with 0.15 mol/L NaCl solution, containing 0.013 mol/L sodium citrate buffer to make the pH 7.4, and mannitol to make the osmolality 300 mOSm. The temperature of the perfusate was 37 C.

Twelve cats underwent perfusion of the gallbladder and 2 hours of infusion of PAF into the hepatic artery. Platelet-activating factor (1-0-alkyl-2-acetyl-SN-glyceryl-phosphoryl choline; Sigma Chemical Co., St. Louis, MO) was maintained in a stock solution of chloroform and, when used, it was evaporated under a stream of nitrogen and reconstituted in 0.25% (W/V) bovine serum albumin in 0.15 mol/L NaCl solution. Three groups of four cats had PAF infused in dosages of 0.5, 0.75, and 1.0 μg kg^{-1} · minute^{-1}.

Four cats underwent perfusion of the gallbladder, and 0.15 mol/L NaCl solution was infused into the hepatic artery. Four cats received 10 mg/kg indomethacin (Sigma) orally by gavage 12 hours before the experiment and 5 mg/kg^{-1} · hour^{-1} indomethacin intravenously throughout the period of gallbladder perfusion.

Four cats received indomethacin intravenously, and PAF 1 μg/kg^{-1} · minute^{-1} into the hepatic artery during 2 hours of gallbladder perfusion. The order of the experiments was randomized.

Gallbladder effusate was collected on ice at 30-minute intervals for measurement of [^{14}C] PEG activity and prostanoid concentrations. [^{14}C] Polyethylene glycol activity was measured, using 200-μl samples of the perfusion solution or effluent, in a liquid scintillation spectrometer, after the addition of 10 mL of Instagel (Packard Instruments, Downers Grove, IL).

At the completion of the experiments, the animals underwent cholecystectomies. The gallbladders were opened and washed gently with 5 mL 0.15 mol/L NaCl solution, and a 0.5 × 0.5-cm segment from the middle of the gallbladder was removed for histologic evaluation after hematoxylin and eosin staining. For pathologic evaluation, two full-thickness sections from different levels of the gallbladder strip were coded and evaluated in a blinded manner by three clinical pathologists, with delineation of the amount of inflammation present by a scoring system. Inflammatory cell infiltrate, edema, and mucosal cell injury were graded on a scale of 0 to 3, with zero being normal and three representing maximal changes. The final histologic score was taken as the total of the scores produced by each pathologist.

Attempts also were made to quantitate gallbladder inflammation by measuring β-glucuronidase and myeloperoxidase activity. These lysosomal enzymes are derived from invading inflammatory cells, and the enzyme concentrations in tissues increase with leukocyte invasion.[16,17] The activity of the enzymes parallels the severity of the inflammation in inflammatory responses[16–18] and in human cholecystitis.[19]

To determine myeloperoxidase activity, a 0.5 × 1-cm piece of gallbladder tissue was weighed and homogenized on ice in 2 mL of 0.5% hexadecyltrimethyl ammonium bromide (HTAB; Sigma), in 50 mmol/L (millimolar) potassium phosphate buffer at pH 6.0. The homogenates were sonicated in an ice bath for 10 seconds and freeze-thawed three times. The homogenates were sonicated again and centrifuged at 12,000*g* for 15 minutes. The supernatant was assayed spectrophotometrically for myeloperoxidase activity by incubating 0.1 mL of the supernatant with 2.9 mL of a solution prepared by dissolving 2.9 mL of O-dianisidine dihydrochloride (Sigma) in 90 mL distilled water and adding 10 mL 50 mmol/L potassium phosphate buffer (pH 6.0) and hydrogen peroxide to a final concentration of 0.0005%. The change in absorbance with time at 460 nm was measured with a spectrophotometer (Beckman Instruments, Fullerton, CA). One unit of myeloperoxidase activity was defined as that degrading 1 μ mole peroxide/minute at 25 C.[20] Results are expressed as units/g wet tissue/minute.

β-glucuronidase was measured using the method described by Giannetto and DeDave[21] after homogenization, using 100 strokes of Dounce homogenizer, of the remaining part of the gallbladder in 1 mL ice-cold 50 mmol/L TRIS HC1 buffer, pH 7.0, containing 2.5 mmol/L ethylenediaminetetraacetic acid (EDTA; Sigma). Protein concentrations in the homogenates were determined by the method of Lowry.[22]

Previous experiments[23] demonstrated that the primary prostanoids produced by feline gallbladder mucosal cells and muscle tissue were PGE and 6-keto $PGF_{1\alpha}$, representing prostacyclin formation.[24] A portion of the same gallbladder homogenates used for measurement of β-glucuronidase activity and the gallbladder effusates were used to extract, separate, and quantitate, by radioimmunoassay, PGE and 6-keto $PGF_{1\alpha}$ concentrations, as described previously.[25]

Statistical analysis was performed by one-way analysis of variance. The significance of the difference between variables was evaluated by Dunnet's t test if the F value was significant at the $p < 0.05$ level. Statistical differences of the histologic scores of inflammation were determined by the Wilcoxon rank-sum test. Throughout the manuscript 'significant' indicates $p < 0.05$.

Results

The hemodynamic changes associated with PAF administration are illustrated in Figure 1. Indomethacin administration alone did not significantly alter heart rate or blood pressure. Platelet-activating factor administration decreased mean arterial pressure from 90 to 60 mmHg in cats receiving PAF alone and PAF plus indomethacin. No significant differences in the hypotensive effects of the three doses of PAF were identifiable; however the number of animals in each group was small. Platelet-activating factor administration was not lethal in any of the 14 cats receiving it. It produced bradycardia and the response appeared to follow uniformly the hypotensive effects (Fig. 1).

The theoretical implication related to measuring gallbladder water transport is that, in normal gallbladder, insorption of water occurs, and in inflamed mucosa exsorption of fluid is evident.[26] Loss of gallbladder fluid absorption is postulated to be an early sign of gallbladder inflammation or cholecystitis.[26]

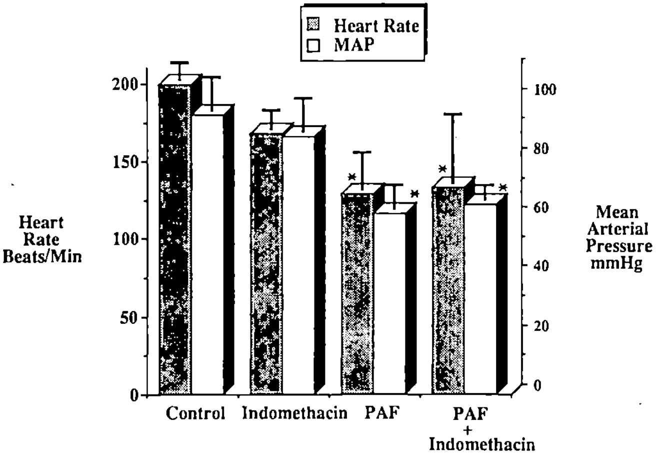

FIG. 1. The effect of PAF on heart rate and blood pressure 60 minutes after the institution of PAF infusion or the same time interval during control experiments. This time period was chosen as representative of the hemodynamic changes produced by the drug (1 $\mu g/kg^{-1} \cdot min^{-1}$). Each bar represents the mean ± SEM of four values from one experiment on each of four cats. Asterisk indicates that the PAF value is significantly different from the control value.

As seen in Table 1, normal gallbladders absorbed approximately 0.4 to 0.8 mL/hour, as measured by concentration changes in a nonabsorbable marker. When indomethacin was administered, gallbladder absorption was disturbed, with some cat gallbladders having reversal of the fluid transport processes and demonstrating exsorption or nearly zero transport of fluid.

Platelet-activating factor administration in all doses produced exsorption of fluid, and the process appeared to be dose related. When 1 $\mu g/kg^{-1} \cdot minute^{-1}$ PAF was administered into the hepatic artery, exsorption of fluid occurred at a rate greater than 1 mL/hour.

Indomethacin was administered along with PAF 1 $\mu g/kg^{-1} \cdot minute^{-1}$, and significantly decreased gallbladder fluid exsorption produced by PAF (Table 1).

Gallbladder perfusate 6-keto $PGF_{1\alpha}$ concentrations (Table 2), were approximately six times greater than perfusate PGE concentrations (Table 3). Indomethacin markedly decreased perfusate prostanoid levels (Tables 2 and 3). Platelet-activating factor did not significantly change gallbladder perfusate 6-keto $PGF_{1\alpha}$ concentrations (Table 2). Prostaglandin E perfusate concentrations were significantly increased by PAF, and the change was inhibited by indomethacin (Table 3). Platelet-activating factor produced significant dose-related increases in gallbladder homogenate 6-keto $PGF_{1\alpha}$ and PGE concentrations, and the changes were inhibited by indomethacin (Table 4).

Platelet-activating factor increased the concentrations of β-glucuronidase in gallbladder homogenates only at the highest dose of PAF administered, and this increase was prevented by the administration of indomethacin

TABLE 1. *The Effect of Platelet-activating Factor ($\mu g/kg \cdot min^{-1}$) and Indomethacin on Gallbladder Mucosal Fluid Transport ($\mu L/30$ minutes)*

	Platelet-activating Factor				
Cat	120 min.	150 min.	180 min.	210 min.	240 min.
Control	−140 ± 90	−200 ± 90	−200 ± 60	−320 ± 80	−420 ± 80
Indomethacin	−100 ± 70	−80 ± 50	−80 ± 100*	−90 ± 50*	−180 ± 50*
PAF					
0.5	−150 ± 70	+280 ± 180	+190 ± 30	+120 ± 100*	+320 ± 170*
0.75	−200 ± 60	+470 ± 120	+41 ± 120*	+190 ± 40*	+410 ± 50*
1.0	−170 ± 50	+660 ± 50	+580 ± 160*‡	+540 ± 60*‡	+720 ± 160*‡
PAF 1.0 + indomethacin	−10 ± 60	+280 ± 0.03	+160 ± 0.12	+170 ± 50*	+190 ± 60*

Each value represents the mean ± SEM of four values obtained from one experiment of four cats. A − sign indicates insorption and a + sign indicates exsorption. Asterisk indicates that the value is significantly different from the control value. ‡ indicates that the PAF value is significantly different from the PAF-plus-indomethacin value. PAF was infused into the hepatic artery through the gastroduodenal artery. Animals receiving indomethacin were pretreated with 10 mg orally 12 hours before the experiment and received 5 $mg/kg^{-1} \cdot hr^{-1}$ intravenously throughout the 4 hours of gallbladder perfusion.

(Table 4). Myeloperoxidase activity was increased at all doses of PAF administration, and the change was prevented by indomethacin (Table 4).

Representative histologic photomicrographs of normal feline gallbladder, feline gallbladder removed after 2 hours of PAF administration (1 $\mu g/kg^{-1} \cdot minute^{-1}$), and a gallbladder removed after PAF and indomethacin administration are presented in Figure 2. The histologic scores of the 10 control gallbladders, including the gallbladders from the five cats receiving indomethacin, were combined and the histologic scores of all nine gallbladders removed from cats receiving PAF were combined. These results were compared to the histologic scores from the gallbladders from the cats receiving PAF and indomethacin. As seen in Figure 2, PAF produced a significant increase in gallbladder inflammation as evaluated by a histologic scoring system, and the inflammatory response was significantly prevented by indomethacin administration.

As a point of reference, the mean ± SEM histologic score of inflammation for the control gallbladders was 2.6 ± 0.4 (n = 8), while the histologic scores for the gallbladders from the cats receiving PAF was 8.6 ± 1.3 (n = 12). Feline gallbladders from animals receiving PAF and indomethacin had a mean histologic score of 2.0 ± 0.5 (n = 4).

Discussion

The data presented in this report suggests that PAF induces inflammatory changes in the feline gallbladder associated with increased prostanoid production in perfusate and gallbladder tissue. Inhibition of cyclooxygenase activity by indomethacin decreased the prostanoid levels and prevented the inflammatory changes associated with PAF administration. This is the fourth model of feline cholecystitis in which the inflammatory process has been shown to be mediated by prostanoids and prevented by cyclooxygenase inhibition. In previous studies exsorption of fluid, cholecystitis, and increased prostanoid levels were produced by intraluminal carrageenan administration,[23] perfusion of the gallbladder with lysophosphatidylcholine

TABLE 2. *The Effect of Platelet-activating Factor ($\mu g/kg^{-1}$ min^{-1}) and Indomethacin on Gallbladder Perfusate 6-Keto $PGF_{1\alpha}$ Concentration (pg/mL)*

	Platelet-activating Factor				
Cat	120 min.	150 min.	180 min.	210 min.	240 min.
Control	339 ± 74	313 ± 79	318 ± 76	285 ± 55	297 ± 51
Indomethacin	58 ± 16*	60 ± 15*	67 ± 15*	62 ± 9	24 ± 7*
PAF					
0.5	424 ± 48	194 ± 38	191 ± 45	257 ± 81	238 ± 20
0.75	391 ± 53	591 ± 105	398 ± 46	360 ± 8	366 ± 30
1.0	521 ± 119	410 ± 88‡	463 ± 73‡	384 ± 42‡	396 ± 43‡
PAF + indomethacin	53 ± 21	60 ± 13	59 ± 21	63 ± 21	65 ± 6

Each value represents the mean ± SEM of four values obtained by perfusing the gallbladder of four cats. Asterisk indicates that the value is significantly different from the control value. ‡ indicates that the PAF value is significantly different from the PAF-plus-indomethacin value.

TABLE 3. *The Effect of Platelet-activating Factor ($\mu g/kg^{-1} \cdot min^{-1}$) and Indomethacin on Gallbladder Perfusate PGE Concentration (pg/mL)*

	Platelet-activating Factor				
Cat	120 min.	150 min.	180 min.	210 min.	240 min.
Control	74 ± 15	68 ± 15	76 ± 13	86 ± 16	57 ± 18
Indomethacin	4 ± 1*	6 ± 0.6	5 ± 0.9*	10 ± 3*	11 ± 5
PAF					
0.5	106 ± 23	46 ± 2	57 ± 10	62 ± 9	74 ± 12
0.75	107 ± 10	57 ± 14	92 ± 33	141 ± 18	118 ± 13*
1.0	99 ± 26	179 ± 52*‡	155 ± 37*‡	190 ± 18*‡	209 ± 25*‡
PAF + indomethacin	13 ± 5	17 ± 6	18 ± 5	16 ± 7*	7 ± 2

Each value represents the mean ± SEM of four values obtained by perfusing the gallbladders of four cats. Asterisk indicates that the value is significantly different from the control value. ‡ indicates that the PAF value is significantly different from the PAF-plus-indomethacin value.

solution,[27] and bradykinin administration,[25] with a decrease in the inflammatory changes produced by administration of cyclooxygenase inhibitors.

Several characteristics of the relationship of experimental cholecystitis to prostanoid formation are different. In cholecystitis induced by bradykinin[25] and PAF, prostanoid levels increased and the gallbladder effusate was clear and contained no measurable protein. Cyclooxygenase inhibition significantly decreased the prostanoid levels and the exsorption of fluid produced by gallbladder mucosa in response to bradykinin[25] and PAF (Table 1). Lysolecithin administration into the lumen of the gallbladder resulted in the outpouring of a protein-rich fluid and an increase in prostanoid levels and cyclooxygenase inhibition decreased the protein secretion and prostanoid levels.[27] All of the models described are associated with gallbladder inflammation. The explanation of why experimental cholecystitis is associated with a protein-rich fluid under certain conditions is unclear.

In humans with acute calculous[19] and acalculous[10] cholecystitis, prostanoid levels are increased and the more severe the inflammation, the greater are the increases in prostanoid levels.[10,19] Administration of cyclooxygenase inhibitors in humans decreases prostanoid levels and relieves the pain of cholecystitis.[28,29] We do not know if cyclooxygenase inhibitors decrease inflammation in human cholecystitis because we have no way to determine the degree of inflammation before cyclooxygenase inhibitors are administered.

We chose to evaluate PAF as a putative shock-associated mediator of acute acalculous cholecystitis, primarily because it has been shown to produce inflammatory changes in other parts of the gastrointestinal tract.[7,30,31] In the stomach and small intestine, PAF-produced inflammatory changes do not appear to be mediated by prostanoids,[30,31] although they may be mediated by leukotrienes.[31]

In the gallbladder, PAF-induced inflammation appears to be mediated by prostanoids, while preliminary evidence suggests that leukotrienes do not play a significant role in the production of feline experimental cholecystitis.[27]

As is evident in Figure 1, PAF administration produces hypotension and bradycardia. It is unclear whether the changes in the gallbladder are the direct response of the gallbladder to PAF or the result of hypotension or other shock-produced factors. The inflammatory changes may be the result of decreased gallbladder blood flow associated with hypotension or due to other substances released dur-

TABLE 4. *The Effect of Platelet-activating Factor ($\mu g/kg^{-1} \cdot min^{-1}$) and Indomethacin on Gallbladder Tissue Prostanoid Formation (ng/mg protein) and β-glucuronidase ($\mu g/mg^{-1} \cdot$ protein hr^{-1}) and Myeloperoxidase Activity (units/g wet tissue/minute)*

Cat	Tissue 6 keto PGF$_{1\alpha}$	Tissue PGE	Beta Glucuronidase	Myeloperoxidase
Control	5.8 ± 1.9	0.4 ± 0.06	55 ± 7	27 ± 10
Indomethacin	0.01 ± 0.001*	0.08 ± 0.001	60 ± 10	21 ± 6
PAF				
0.5	14 ± 0.6*	1.8 ± 0.2*	59 ± 1	88 ± 2*
0.75	19 ± 0.4*	2.0 ± 0.003*	68 ± 7	102 ± 4*
1.0	22 ± 0.2*‡	3.0 ± 0.2*‡	86 ± 8*‡	148 ± 2*‡
PAF 1.0 + indomethacin	0.06 ± 0.03*	0.04 ± 0.008*	31 ± 7	57 ± 10*

Each value represents the mean ± SEM of four values obtained from one experiment on four cats. Asterisk indicates that the value is significantly different from the control value. ‡ indicates that the PAF value is significantly different from the PAF-plus-indomethacin value.

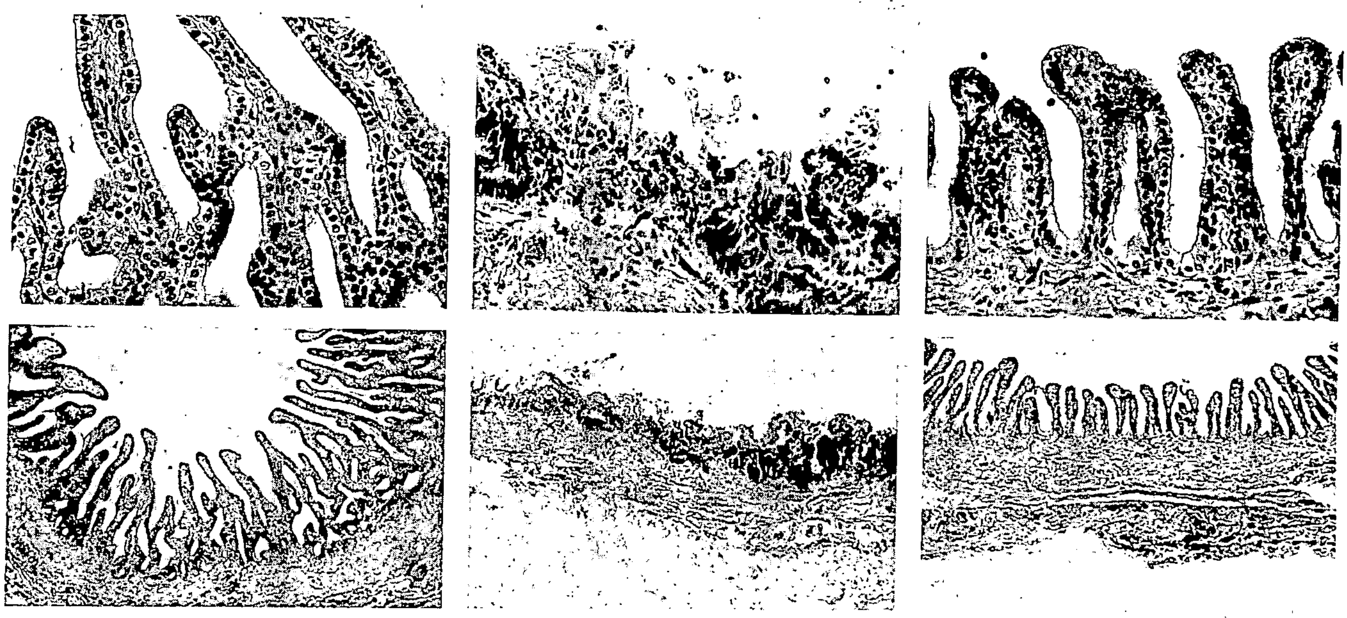

FIG. 2. Photomicrographs of histologic sections of feline gallbladders stained with hematoxylin and eosin (100× and 400×). Buffer-perfused gallbladders (left) had normal histologic appearance with villous mucosa and no wall thickening or inflammatory cell infiltrate. Gallbladders from cats receiving PAF (center) had damaged mucosa, inflammatory cell infiltration, and thickened wall with focal hemorrhage. Minimal discernible histologic inflammation was present when gallbladders from cats treated with PAF and indomethacin (right) were compared to gallbladders from cats treated with PAF alone (center).

ing hypotension. It will be important to determine if hemorrhagic and endotoxin shock and administration of other mediators of the acute-phase reaction, such as interleukin 1, tumor necrosis factor α, and hepatocyte-stimulating factor (interleukin 6),[32–34] are associated with the production of gallbladder inflammation. Platelet-activating factor administration in other systems increases the formation and release of these substances. It is possible that PAF produces gallbladder inflammation indirectly by stimulation of the formation and release of interleukin 1,[32] tumor necrosis factor,[32] or interleukin 6.[33]

The demonstration that PAF induces cholecystitis after administration into the cystic artery supports the concept that PAF may play a role in the development of acute acalculous cholecystitis following shock.[9] As is true with other inflammatory processes that occur in the gallbladder, the response appears to be mediated by prostanoids.

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Discussion

Dr. David Nahrwold (Chicago, Illinois): Dr. Kaminski and his group have shown that platelet-activating factor produces acute cholecystitis as well as secretion of fluid into the lumen of the gallbladder, in contrast to the normal absorption of fluid from the gallbladder. It is not clear whether the hypotension produced by platelet-activating factor causes the cholecystitis, or whether the platelet-activating factor itself causes it, and I would like to ask Dr. Kaminski to give us his opinion about this.

Have you produced acute cholecystitis with other agents in the absence of hypotension?

Finally, inasmuch as the inflammation can be ameliorated by cyclooxygenase inhibitors, what are your thoughts about their possible use as prophylaxis against acute acalculous cholecystitis in critically ill, intensive care unit patients?

Dr. Charles K. McSherry (New York, New York): Approximately 10 or 12 years ago, Dr. Glenn and the group at Cornell were able to produce acalculous cholecystitis in dogs by a variety of stimuli given by aerosol spray or by injection.

All of these stimuli had as a common final pathway derangements of the clotting cascade, particularly the impairment of the function of Hagamen factor or factor XII, and I ask Dr. Kaminski and his coauthors if they have any information on the role of the platelet factor on the clotting cascade as a possible intermediary to the development of acalculous cholecystitis.

Dr. Leonard Rosoff (Livingston, Montana): This excellent presentation brought to mind a study done a number of years ago with my predecessor and mentor, Dr. C. J. Berne, in a large public hospital to evaluate early operation *versus* delayed operation for acute cholecystitis.

As a part of the study, the contents of the gallbladder were aspirated in each patient immediately before removal. In addition to bacteriologic and cytologic studies, enzyme studies were done by the late Dr. Jack Haverback in his research laboratories.

In approximately 11 or 12 patients, I don't recall the precise number at this time, in whom no stones were found, the pancreatic enzymes in the gallbladder were markedly increased compared to the patients with cholelithiasis. Subsequently we used the term 'acute enzymatic cholecystitis' rather than 'acute acalculous cholecystitis.'

Can the authors of this paper see any correlation of the increased prostaglandins in the tissues of the gallbladder to the significant increase in pancreatic enzymes in the gallbladder bile of patients with acute calculous cholecystitis?

Dr. D. Kaminski (Closing discussion): The question of whether cyclooxygenase inhibitors can prevent the development of acalculous cholecystitis is an important one. Recently a patient who underwent a cholecystectomy for acalculous cholecystitis for a gangrenous gallbladder was treated with a large dose of steroids before the development of gallbladder disease. Although this represents an anecdotal observation on our part, it suggests that cyclo-oxygenase inhibitors will not uniformly prevent acalculous cholecystitis.

Dr. Nahrwold is correct in indicating that the effect of shock is not known. Platelet-activating factor administration produces hypotension, which alone may induce the gallbladder changes we demonstrated. Also the effects of other cytokines and monokines, present in the blood stream in shock, on the gallbladder are not known and these substances may contribute to the development of acalculous cholecystitis.

Dr. McSherry is correct. The effects of platelet-activating factor in other systems in producing inflammatory changes seems to be associated with the development of arteriolar thrombosis resulting in impaired blood flow. I believe this was an important aspect of the histologic changes we identified in this study.

Dr. Rosoff asked if there were substances present in the gallbladder that produce chemical cholecystitis. One of the more important proinflammatory substances present in gallbladder bile that produces experimental cholecystitis is lysolecithin. I suspect that patients who develop acute acalculous cholecystitis have many factors present in their gallbladders that can cause inflammation.

Multiple Cytokines Are Required to Induce Hepatocyte Nitric Oxide Production and Inhibit Total Protein Synthesis

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The etiology and mechanisms by which severe trauma or sepsis induce hepatic failure are unknown. Previously we showed that Kupffer cells (KC), the fixed macrophages of the liver, induce a profound decrease in hepatocyte (HC) total-protein synthesis when exposed to endotoxin. Furthermore we demonstrated that endotoxin-activated KCs induce these changes in HC protein synthesis through the induction of a novel L-arginine–dependent biochemical pathway within the HC. In this pathway, the guanido nitrogen of L-arginine is converted to the highly reactive molecule nitric oxide (NO·). To identify the KC factors that act as signals for induction of HC NO· biosynthesis, recombinant cytokines were added to HC cultures and HC nitrogen oxide production and protein synthesis levels were determined. We found that no single cytokine, but rather a specific combination of tumor necrosis factor, interleukin-1, interferon-gamma, and endotoxin, were required for maximal induction of HC nitrogen oxide production. This specific combination of cytokines induced a 248.8 ± 26.0 μmol/L (micromolar) increase in HC nitrogen oxide production and simultaneously inhibited HC total protein synthesis by 36.1% ± 3.1%. These data demonstrate that multiple cytokines, produced by endotoxin-activated KC, induce the production of NO· within HC, which in turn leads to the inhibition of HC total-protein synthesis.

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SIGNIFICANT CHANGES IN hepatic function occur in surgical patients after severe trauma, extensive operations, and in sepsis. Some of these changes in metabolism, such as the hepatic acute-phase response, are clearly physiologic and adaptive, whereas other changes appear to be pathologic, most clearly the hepatocellular dysfunction accompanying multisystem organ failure. Many advances have been made toward the supportive management of the hepatic failure associated with sepsis, but very little is known of the etiology or mechanisms by which this hepatocellular dysfunction occurs. We have hypothesized that Kupffer cells (KC), the fixed macrophages of the liver, interact with septic stimuli within the portal circulation and respond by producing mediators that alter the function of contiguous hepatocytes (HC) in sepsis. In support of this hypothesis, we have demonstrated in a rat HC:KC coculture model that KC activated by endotoxin (lipopolysaccharide, LPS) or killed *Escherichia coli* induce a profound decrease in HC total-protein synthesis.[1,2] Furthermore we identified a novel L-arginine biochemical pathway as the mechanism by which these changes in HC protein synthesis occur.[3–5] In this pathway, a guanido nitrogen of L-arginine is oxidized to form the highly-reactive molecule nitric oxide (NO·), which, in the presence of oxygen and water, rapidly decomposes to the stable and inactive end products, nitrite and nitrate (NO_2^-/NO_3^-).[6–8] Recently we demonstrated that conditioned medium from interferon-gamma (IFNg)- and LPS-activated KC induce the conversion of large quantities of L-arginine to NO· within HC, which, in turn, leads to the inhibition of HC total-protein synthesis.[9] The studies reported here were undertaken to determine the KC factors that act as signals for induction of HC NO· biosynthesis.

Materials and Methods

Reagents

Liver cell cultures were performed in Williams medium E (0.24 mmol/L [millimolar] L-arginine) supplemented

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with 15 mmol/L HEPES, 2 mmol/L L-glutamine, 10^5 U/L penicillin, 100 mg/L streptomycin (Gibco, Grand Island, NY), 10^{-6} mol/L (molar) bovine insulin (Eli Lilly Co., Indianapolis, IN), and 10% heat-activated, low endotoxin calf serum (Hyclone Laboratories, Logan, UT). Hepatocyte culture medium was also supplemented with 10^{-6} mol/L dexamethasone (Sigma Chemical Co., St. Louis, MO). Recombinant rat IFNg (rrIFNg) was purchased from Amgen Biologicals (Thousand Oaks, CA) and recombinant human interleukin 1 beta (rhIL-1) from Cistron Technology (Pine Brook, NJ). Recombinant murine tumor necrosis factor-alpha (rmTNFα) and recombinant human interleukin 6 (rhIL-6) were obtained from Genzyme Corporation (Cambridge, MA). L-[4,5-^{3}H(N)] leucine (^{3}H-leu, specific activity 5.0 Ci/mmol/L) and [methyl-^{3}H] thymidine (^{3}H-thymidine, specific activity 6.7 Ci/mmol/L) were from New England Nuclear (Boston, MA). Lipopolysaccharide (from *E. coli*, 0111:B$_4$) was obtained from Difco Laboratories (Detroit, MI). N^G monomethyl-L-arginine (NMA) was prepared according to the method of Corbin and Reporter[10] modified as previously described.[11]

Cell Isolation

Liver cells were obtained from male Sprague-Dawley rats that weighed 200 to 300 g (Harlan Sprague-Dawley, Madison, WI). Hepatocytes were harvested using a modification of the Seglan perfusion technique,[12] as previously described.[1] The liver was perfused *in situ* with a 0.05% collagenase solution (Type IV, Sigma) for 20 minutes. After perfusion the capsule of the liver was dissected and the parenchyma gently combed to produce a cell suspension. Hepatocytes then were separated from nonparenchymal cells to more than 98% purity[13] by repeated differential sedimentation at 50*g* for 2 minutes and washing with medium. The HCs were enumerated and viability was consistently more than 85% by trypan blue exclusion.

Liver nonparenchymal cells, which by definition include KC, endothelial cells, Ito cells, and pit cells, were obtained using the pronase perfusion technique of Einess and Planque,[14] as previously described.[15] The liver was perfused *in situ* for 2 minutes with Gey's balanced salt solution (Gibco) containing 0.2% pronase E (Sigma). The liver was then minced into 2- to 3-mm cubes and incubated with continuous stirring for 60 minutes at 37 C. DNase (1 mg, Sigma) was added after 20 and 40 minutes to prevent cell clumping. The liver slurry was filtered through gauze mesh, washed in cold RPMI, and centrifuged at 250*g* for 5 minutes. Centrifugal elutriation was performed to separate the KCs from the other nonparenchymal cells. Viability exceeded 98% by trypan blue exclusion and peroxide staining of the cell suspension identified 85% to 95% of the cells as KCs.

Cell Culture Technique

Conditioned KC supernatants were generated by plating 6×10^6 KC in 3 mL in 25-cm^2 flasks (Costar Data Packaging Co, Cambridge, MA). During the initial incubation, the KCs were cultured in standard medium or medium supplemented with rrIFNg 100 units/mL. After 24 hours the medium was aspirated and replaced with fresh medium containing rrIFNg (100 U/mL) and LPS (10 μg/mL) or LPS alone. After the addition of LPS, the KC supernatants were collected at various time intervals, filtered through 0.2-μm pore-size filters, and stored at -70 C until use.

Hepatocytes were plated in supplemented Williams medium E at a concentration of 2×10^5 cells/mL on gelatin-coated 96-well tissue culture trays (0.1 mL/well) for determination of total protein synthesis, and in 35-mm wells (2 mL) for measurement of NO_2^-/NO_3^- production. Following an initial 18-hour incubation, the medium on the HC cultures was aspirated and KC supernatant (50% dilution), rrIFNg, rhIL-1, rmTNFa, rhIL-6, and/or LPS was added. Hepatocyte total-protein synthesis and NO_2^-/NO_3^- production were assessed after 24 hours of exposure to KC supernatant or recombinant cytokines.

Total-protein Synthesis and NO_2^-/NO_3^- Determination

Hepatocyte total-protein synthesis was measured using a 4-hour labeling interval with ^{3}H-leu (1.0 μCi/well) added in fresh Minimal Essential Medium without L-leucine (Gibco). The label was terminated by lysing the HC with 1 N NaOH and 0.025% triton X-100. The protein was precipitated with cold 40% trichloroacetic acid and collected on filter paper using a multichannel cell harvester. ^{3}H-leu incorporation into protein was measured by liquid scintillation counting. The NO_2^-/NO_3^- concentration of the HC culture supernatants was measured using an automated colorimetric procedure based on the Griess reaction.[16]

Cytokine Assays

TNF. Kupffer cell production of TNF *in vitro* was determined with the lytic assay of L929 fibroblasts, as described by Aggarwal.[17] Briefly serial dilutions of the KC supernatants were added to murine L929 cells cultured in the presence of actinomycin D. After an 18-hour incubation, the cultures were washed and the degree of cell lysis was determined by staining the plates with 0.5% crystal violet in methanol/water. The optical density of the L929 cultures was measured at 560 nm and the quantity of TNF in the conditioned KC supernatants determined from standard curves generated for each experiment using rmTNFα.

Interleukin 1. Interleukin 1 activity in the KC supernatants was determined in the D10.G4.1 cell proliferative assay.[18] Serial dilutions of KC supernatant and 2.5 μg/mL concanvalin A were added to 2×10^4 D10.G4.1 cells. After a 65-hour incubation, the cultures were labeled with 2 μCi/well of ^3H-thymidine for 6 hours. The cultures were harvested into filter paper and ^3H-thymidine incorporation onto DNA was measured by liquid scintillation counting. The concentration of IL-1 in the KC supernatants was extrapolated from standard curves generated for each experiment using rhIL-1.

Interleukin 6. The B-9 hybridoma, provided by Dr. R. Nordan (National Institutes of Health, Bethesda, MD), was used to measure IL-6 activity.[19] Briefly 2×10^3 cells were cultured in the presence of serial dilutions of the KC supernatant for 3.5 days. The cultures were labeled with ^3H-thymidine (2 μCi/well) for 4 hours and ^3H-thymidine incorporation into DNA was determined. The IL-6 activity in the KC supernatants was determined from standard curves constructed with rhIL-6.

Results

Previously we demonstrated that conditioned medium from activated KCs induces HC NO· production and suppresses HC total-protein synthesis.[9] To generate this active KC supernatant, it was necessary to expose the KC to rrIFNg for 24 hours before the addition of LPS. This rrIFN and LPS-activated KC supernatant harvested 8 hours after the addition of LPS induced a 284 ± 7.7 μmol/L (micromolar) increase in HC NO_2^-/NO_3^- production and simultaneously inhibited HC total-protein synthesis by 42.1% ± 3.3% (Fig. 1). If harvested later, 24 and 36 hours after the addition of LPS, the KC supernatant was less active, inducing lower amounts of NO_2^-/NO_3^- production by HC and inhibiting protein synthesis to a lesser degree. While LPS alone is sufficient stimulus to induce L-arginine metabolism to NO· in KC:HC cocultures,[3-5] KC supernatants generated with LPS alone stimulated only a modest increase (56 to 110 μmol/L) in HC NO_2^-/NO_3^- production and had no effect on HC protein synthesis. Therefore maximal induction of HC NO· production and inhibition of total-protein synthesis were dependent not only on the presence of both rrIFNg and LPS but also on a precise interval at which the KC supernatant was collected after stimulation.

There were two possible hypotheses to explain the need for IFNg in the generation of an active KC supernatant. The first possibility was that IFNg may have been acting on the KC to stimulate the synthesis of one or more KC factors, which were, in turn, needed to induce NO· biosynthesis by the HC. A second alternative hypothesis was that IFNg could act directly on the HC, functioning as one of the signals for induction of HC NO· production.

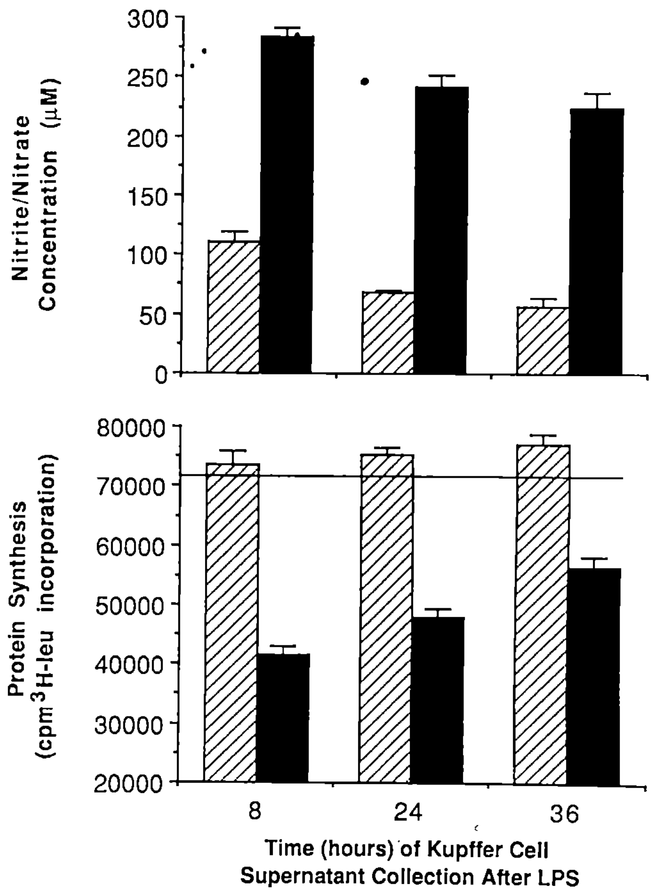


FIG. 1. HC NO_2^-/NO_3^- production and total-protein synthesis in response to KC supernatants generated under different conditions. KC supernatants were generated with the combination of rrIFNg and LPS (■) or LPS alone (▨) and then collected at various time intervals after the addition of LPS. Results are the mean ± SEM of one of three similar experiments in which the KC supernatants were generated in duplicate and then added to quadruplicate HC cultures. The total-protein synthesis of HC cultured in medium alone (——) is shown as a reference. The NO_2^-/NO_3^- concentration in control HC cultures was 2.2 ± 0.6 μmol/L. HC NO_2^-/NO_3^- production and protein synthesis in response to the KC supernatant generated with rrIFNg and LPS were significantly different ($p < 0.05$) from that of the medium control and HC cultures exposed to KC supernatant generated with LPS alone.

To test the first hypothesis, we examined the effects of rrIFNg on KC cytokine production. It is known that IFNg enhances macrophage production of certain cytokines, such as IL-1, while inhibiting the production of other macrophage products, such as PGE_2.[20] Consistent with the literature, higher levels of TNF, IL-1, and IL-6 were found in the KC supernatants activated with rrIFNg and LPS, as compared to the KC supernatants generated with LPS alone (Table 1). Exposure to rrIFNg significantly increased the IL-1 activity in the KC supernatant at all three time points tested. In addition rrIFNg induced a significant early increase in IL-6 levels, following which the levels remained elevated at the later time points. The effects of rrIFNg on TNF levels were less dramatic. While exposure to rrIFNg resulted in slightly greater TNF activity at all

TABLE 1. *Cytokine Levels in KC Supernatants Generated with rrIFNg and LPS or LPS Alone at Varying Time Intervals After the Addition of LPS*

Time (Hours) of KC Supernatant Collection After LPS Exposure	rrIFNg (100 μ/mL)	Cytokine Levels (units/mL)*		
		IL-1	IL-6	TNF
8	–	3.1 ± 0.2	163.2 ± 8.3	363.5 ± 35.8
	+	4.1 ± 0.3†	469.1 ± 21.3†	445.4 ± 36.6
24	–	4.1 ± 0.2	310.5 ± 24.0	286.7 ± 10.2
	+	6.0 ± 0.3†	444.0 ± 21.9	317.4 ± 30.7
36	–	4.7 ± 0.3	454.7 ± 8.9	111.1 ± 11.8
	+	6.4 ± 0.2†	525.7 ± 24.3	240.6 ± 26.1†

* Results are expressed as the mean ± SEM.

† $p \leq 0.05$ when compared with the paired value using the Student's t test.

times tested, only the differences observed at 36 hours were significant. More importantly TNF levels were highest at the 8-hour time and then declined, an activity pattern that is similar to that of the KC supernatant. In contrast IL-1 and IL-6 activity could be detected at 8 hours but peaked at later times. Thus rrIFNg enhanced KC cytokine production but qualitatively all of the cytokines tested were present in measurable quantities, whether the KCs were exposed to rrIFNg and LPS or to LPS alone.

To determine if IFNg might be required as one of the signals directly influencing the HC response, rrIFNg was added directly to the HC cultures with a KC supernatant prepared using only LPS as a stimulating agent. The LPS-activated KC supernatant had minimal activity alone, but when added to HC with rrIFNg it induced significant increases in HC NO_2^-/NO_3^- production and decreases in protein synthesis. These changes were dependent on the rrIFNg concentration (Fig. 2) so that at the highest rrIFNg concentration tested (100 U/mL) a 258.4 ± 4.2 μmol/L increase in the NO_2^-/NO_3^- concentration and 39.7% ± 3.4% decrease in the protein synthesis of the HC cultures were observed. The suppression of HC protein synthesis and increase in NO_2^-/NO_3^- production induced by adding rrIFNg (100 U/mL) directly to the HC cultures, together with the LPS-activated KC supernatant, were not significantly different from that observed with the originally described rrIFNg- and LPS-activated KC supernatant. Adding IFNg (100 U/mL) to the HC cultures alone had no effect on total-protein synthesis and induced only a 1.9 ± 0.4 μmol/L increase in NO_2^-/NO_3^- production, demonstrating that rrIFNg alone was not responsible for the changes. These data indicate that rrIFNg not only increases KC cytokine production but also functions directly on the HC as one of the signals inducing HC L-arginine metabolism to NO•. In addition the data also show clearly that maximal induction of HC L-arginine metabolism to NO• requires more than one factor because neither rrIFNg nor the LPS-activated KC supernatant alone were sufficient stimuli.

To identify the factors within the LPS-activated KC supernatant that were acting in concert with rrIFNg to stimulate HC L-arginine metabolism to NO•, recombinant cytokines were added to the HC cultures with rrIFNg

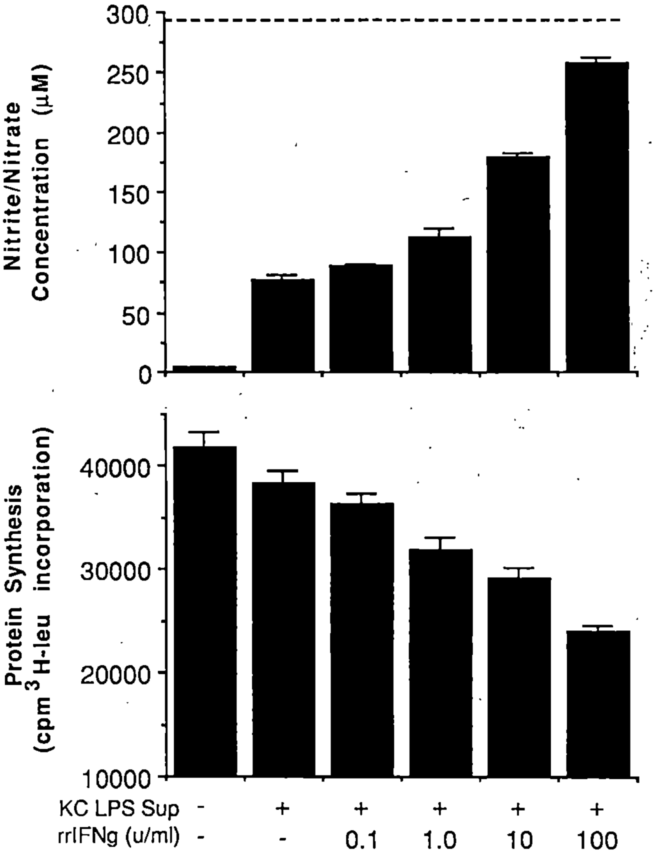


FIG. 2. Concentration-dependent effects of rrIFNg on HC NO_2^-/NO_3^- production and total-protein synthesis. rrIFNg was added directly to HC cultures in combination with LPS-activated KC supernatant and NO_2^-/NO_3^- production and protein synthesis assessed after 24 hours. Results are the mean ± SEM of quadruplicate cultures from one of four similar experiments. HC NO_2^-/NO_3^- production in response to the KC supernatant generated with both rrIFNg and LPS is shown as a reference (---). Significant differences ($p < 0.05$) in HC NO_2^-/NO_3^- production and total-protein synthesis were observed at rrIFNg concentrations ≥ 1.0 U/mL when compared to medium controls or HC cultures exposed to LPS-activated KC supernatant alone.

TABLE 2. *Effect of rrIFNg in Combination with Recombinant Cytokines or LPS on HC NO_2^-/NO_3^- Production and HC Total-protein Synthesis*

HC Culture Additive	Concentration	rrIFNg (100 U/mL)	Protein Synthesis* (cpm ^{3}H-leu Incorporation)	NO_2^-/NO_3^- (μmol/L)*
None	—	–	47,803 ± 2419	1.5 ± 0.1
		+	48,741 ± 1056	1.9 ± 0.4
rmTNF	100 U/mL	+	45,737 ± 1521	21.4 ± 1.2†
	500 U/mL	+	45,699 ± 1074	42.6 ± 2.4†
rhIL-1	1.0 U/mL	+	52,550 ± 2221	8.7 ± 1.7†
	5.0 U/mL	+	51,004 ± 1237	46.4 ± 2.0†
rhIL-6	100 U/mL	+	48,399 ± 796	11.7 ± 0.6†
	250 U/mL	+	54,309 ± 1027	38.1 ± 2.8†
LPS	1.0 U/mL	+	46,532 ± 1148	3.0 ± 0.4†
	10.0 U/mL	+	43,831 ± 817	30.2 ± 1.0†

* Results are expressed as the mean ± SEM.

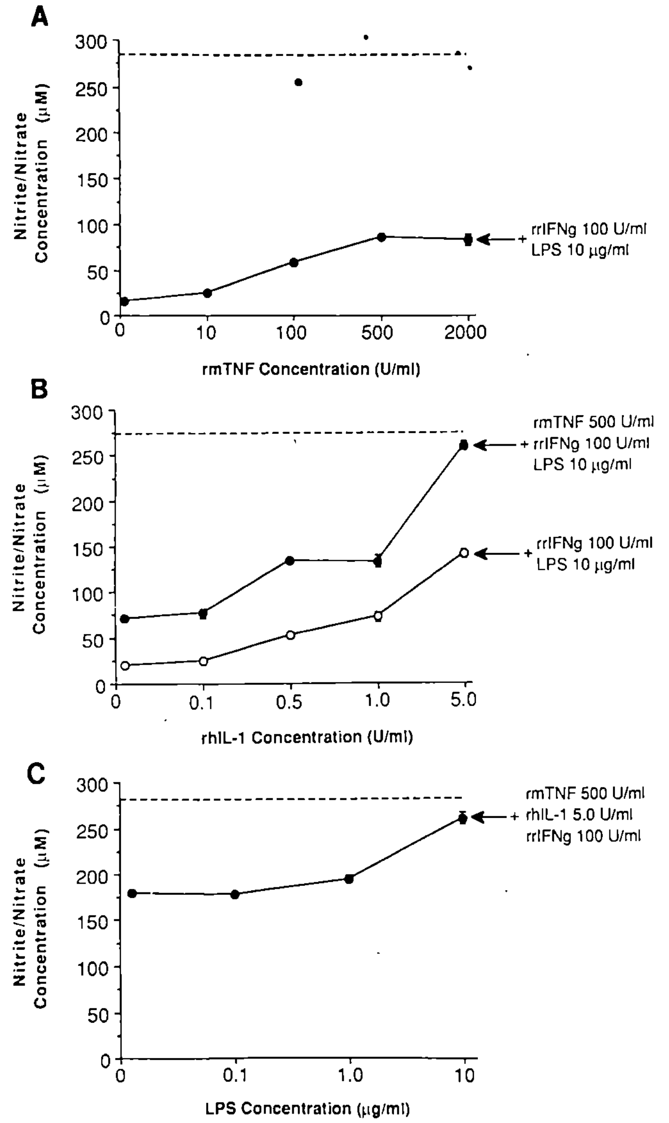
† $p \leq 0.05$ when compared to HC cultured in median alone using the Student's t test.

(Table 2). Addition of any single cytokine, *i.e.*, either rmTNF or rhIL-1 or rhIL-6 or LPS, at concentrations present within the LPS-activated KC supernatant to HC cultures with rrIFNg (100 U/mL) induced only minimal increases in NO_2^-/NO_3^- production. Furthermore these minor increases in HC NO_2^-/NO_3^- production were not associated with any significant suppression of HC protein synthesis. In fact, at the highest concentration of rhIL-6 tested (250 U/mL), the combination of rhIL-6 and rrIFNg actually increased HC total-protein synthesis by 13.6% ± 1.9%. Hepatocyte protein synthesis also was increased slightly in the presence of IL-1 and rrIFNg. Therefore neither LPS nor any single cytokine alone or in combination with rrIFNg could reproduce the increase in HC NO· synthesis and decrease in protein synthesis observed with rrIFNg- and the LPS-activated KC supernatant. However each of the factors functioned synergistically with rrIFNg to induce small but measurable increases in HC NO_2^-/NO_3^- production.

The maximal induction of HC NO_2^-/NO_3^- production was found to require the combination of several factors, including rrIFNg, rmTNF, rhIL-1, and LPS. As illustrated in Figure 3A, rmTNFa induced a concentration-dependent increase in HC NO_2^-/NO_3^- synthesis when added to HC cultures in combination with rrIFNg and LPS. At a rmTNF concentration of 500 U/mL, this combination of factors induced an 86.1 μmol/L ± 1.9 increase in HC NO_2^-/NO_3^- production, nearly two times higher than that observed with the combination of any two factors. Furthermore Figure 3B shows that addition of rhIL-1 to this combination resulted in even greater increases in HC NO_2^-/NO_3^- production to levels near that induced by rrIFNg and the LPS-activated KC supernatant. As observed with rmTNF, induction of HC NO_2^-/NO_3^- biosynthesis by rhIL-1 was concentration dependent, with maximal HC NO_2^-/NO_3^- production requiring 5 U/mL of IL-1. If rmTNF was omitted from this combination of cytokines plus LPS, HC NO_2^-/NO_3^- production decreased from 259.8 ± 5.2 μmol/L to 141.2 ± 4.8 μmol/L. Similarly omitting LPS from the combination of rmTNF, rhIL-1, and rrIFNg resulted in a 79.8 ± 2.1 μmol/L decrease in HC NO_2^-/NO_3^- production (Figure 3C). Unlike the cytokines that induced a concentration-dependent increase in HC NO_2^-/NO_3^- production, LPS stimulation of HC NO· synthesis occurred only at concentrations of 10 μg/mL or more.

The cytokine- and LPS-induced increase in HC NO_2^-/NO_3^- production was associated with a decrease in total-protein synthesis. This is demonstrated in Figure 4, in which the addition of rhIL-1 to the combination with rmTNF, rrIFNg, and LPS induced a concentration-dependent inhibition of HC total-protein synthesis. At the highest concentration tested (5 U/mL), rhIL-1, in combination with these other factors, suppressed HC total-protein synthesis by 36.1% ± 3.1%, which is similar to that observed with the combination of rrIFNg and the LPS-activated KC supernatant. It should be noted also that while the mixture of cytokines and LPS induced both HC NO_2^-/NO_3^- production and inhibited protein synthesis, these effects were not completely parallel. Maximal induction of HC nitrogen oxide synthesis required an rhIL-1 concentration of 5 U/mL, whereas the inhibition of protein synthesis induced by the combination of cytokines was near maximal on exposure to 0.5 U/mL of IL-1, suggesting that a threshold level of NO· production was required to induce the suppression in protein synthesis.

To confirm that the increase in HC NO_2^-/NO_3^- production and inhibition of total-protein synthesis induced by the combination of rmTNF, rhIL-1, rrIFNGg, and LPS were mediated *via* the production of NO·, we added these cytokines to HC cultures in the presence of NMA, a competitive inhibitor of L-arginine metabolism to NO·.[21] NMA (1.0 mmol/L) had no effect on the normal levels of protein synthesis and NO_2^-/NO_3^- production of unstimulated HC. However, in HC cultures exposed to the



FIGS. 3A–C. Concentration-dependent effects of (A) rmTNF, (B) rhIL-1, and (C) LPS on HC NO_2^-/NO_3^- production. The indicated cytokine and LPS combinations were added to HC cultures for 24 hours and the culture supernatants collected for determination of NO_2^-/NO_3^- concentration. The results for each combination are the mean ± SEM of three separate experiments each with triplicate cultures. Where error bars are not shown, they fall within the symbols. HC NO_2^-/NO_3^- production in response to the combination of rrIFNg (100 U/mL) and the LPS-activated KC supernatant is shown as a reference (---). Significant increase ($p < 0.05$) in HC NO_2^-/NO_3^- production occurred at (A) rmTNF concentrations > 100 U/mL, (B) rhIL-1 concentrations ≥ 0.5 U/mL, and (C) at 10 µg/ml of LPS.

combination of cytokines and LPS, or rrIFNg and the LPS-activated KC supernatant, NMA totally blocked the increase in HC NO_2^-/NO_3^- production and substantially reversed the suppression of HC protein synthesis (Table 3). These data indicate that similar to the KC supernatant, the combination of rmTNF, rhIL-1, rrIFNg, and LPS induced HC NO_2^-/NO_3^- production and inhibited total-protein synthesis *via* the conversion of L-arginine to NO•.

Discussion

In 1985 Stuehr and Marletta[22] demonstrated that mammalian cells, specifically macrophages, produce nitrogen oxides when stimulated with interferon gamma (IFNg) and endotoxin. Hibbs et al.[21,23] and Iyengar et al.[24] went on to show in 1987 that L-arginine is the substrate for macrophage nitrite and nitrate (NO_2^-/NO_3^-) production *via* a novel biochemical pathway in which L-arginine in converted to L-citrulline. It has been shown since then that the highly reactive molecule nitric oxide is formed as a short-lived intermediate in this pathway.[6–8] Since the original description in macrophages, a number of other cell types, including endothelial cells,[25–27] neutrophils,[28,29] cerebellar neurons,[30–32] murine EMT-6 adenocarcinoma cells,[33,34] KCs,[3–5] and HCs[9] have been shown to produce NO• from L-arginine. These cell types vary not only in timing and quantity of NO• production but also in the signals that stimulate the cells. Endothelial cells are triggered by vasoactive stimuli such as acetylcholine, bradykinin, and histamine. Neutrophils respond to leukotriene B_4, f-met-leu-phe, and platelet-activating factor, while brain NO• production occurs when L-glutamate binds to N-methyl-D-aspartate receptors on the cerebellar neurons. In these three cell types, expression of the NO• synthase enzyme appears to be constitutive, requiring no previous induction period, and stimulation results in the instantaneous production of small quantities of NO•. In contrast, macrophages, HCs, and murine EMT-6 adenocarcinoma cells synthesize NO• only in response to a specific combination of multiple immunostimulants, which seem not only to stimulate enzyme activity but also may be required to induce the enzyme. In these cells

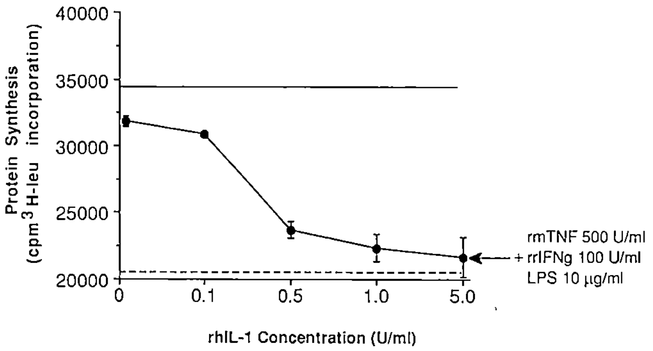


FIG. 4. Concentration-dependent effects of rhIL-1 in combination with rmTNF, rrIFNg, and LPS on HC total-protein synthesis. Increasing concentrations of rhIL-1 were added to HC cultures in combination with rmTNF, rrIFNg, and LPS for 24 hours and HC total-protein synthesis determined. Results are the mean ± SEM of three separate experiments each with quadruplicate cultures. Where error bars are not shown, they fall within the symbols. Control HC total-protein synthesis (——) and the protein synthesis following exposure to the combination of rrIFNg (100 U/mL) and the LPS-activated KC supernatant (---) are shown as a reference. When compared to medium controls, significant decreases ($p < 0.01$) in HC total-protein synthesis were observed at rhIL-1 concentrations ≥ 0.5 U/mL.

TABLE 3. *Effect of NMA on KC Supernatant and Recombinant Cytokine Induction of HC NO_2^-/NO_3^- Production and the Inhibition of HC Total Protein Synthesis*

HC Culture Conditions	NMA (1.0 mmol/L)	Protein Synthesis* (cpm ^{3}H-leu incorporation)	NO_2^-/NO_3^- (μmol/L)*
Medium	−	43796 ± 1847	3.1 ± 1.0
	+	43309 ± 3108	3.5 ± 1.9
KC supernatant	−	24564 ± 1612 (44)†‡	237.7 ± 20.4‡
	+	40606 ± 1241 (7)†	3.3 ± 0.4
rmTNF/rhIL-1/rrIFNg/LPS	−	27970 ± 2953 (36)†‡	248.8 ± 26.0‡
	+	39974 ± 2747 (9)†	3.8 ± 2.0

* Results are expressed as the mean ± SEM.

† The percent suppression compared to HC cultured in medium alone.

‡ $p \leq 0.05$ when compared to HC cultured in medium alone using the Student's t test.

induction of NO• synthase requires 4 to 18 hours of exposure to cytokines and/or bacterial endotoxin, following which larger quantities of NO• are produced. In this report we demonstrated that rTNF, rhIL-1, rrIFNg, and LPS act synergistically to induce maximal HC L-arginine metabolism to NO•. While these signals are similar to those required to induce maximal EMT-6 adenocarcinoma cell NO• production, they differ from that of macrophages. For example although rhIL-1 is a potent synergistic signal for HC, it has no effect on macrophage production of NO_2^-/NO_3^-.[35] Also dexamethasone, which inhibits the induction of macrophage NO• synthase,[36] has no effect on induction of HC NO_2^-/NO_3^- production (data not shown). Therefore, while these different cell types all produce NO• *via* a similar biochemical pathway, the specific stimuli for the induction of the NO• synthase enzyme within these cells appears to be relatively cell specific.

The physiologic significance of mammalian cell NO• biosynthesis is only beginning to be elucidated. *In vitro* endothelial cell-derived NO• has been shown to activate soluble guanylate cyclase in smooth muscle cells, leading to an increase in intracellular cGMP levels.[26] Through this mechanism, endothelial-derived NO• induces the relaxation of adjacent vascular smooth muscle, thereby decreasing vascular tone.[25–27] Consistent with these *in vitro* findings, Aisaka et al.[37] and Vallance et al.[38] showned that the *in vivo* administration of NMA, the competitive inhibitor of NO• synthase, results in arterial hypertension that is reversible with L-arginine. This suggests that ongoing endothelial NO• synthesis plays an important role in the regulation of vascular tone and blood pressure. Through the activation of soluble guanylate cyclase, NO• biosynthesis also appears to play a role in signal transduction within the central nervous system[31–33] and in the regulation of neutrophil chemotaxis.[11] *In vitro* NO• generated by macrophages has been shown to inactivate complex I and complex II of the electron transport chain[7,39] and the Krebs cycle enzyme aconitase.[21] This NO•-mediated inhibition of mitochondrial respiration is thought to be one mechanism by which activated macrophages inhibit the growth of some tumor cells[21,23,39] and microorganisms.[40,41] In this report we demonstrated that HC NO• synthesis is associated with a profound decrease in HC total-protein synthesis. We also showned that authentic NO• inhibits not only HC total protein synthesis but also the production of specific proteins (albumin and fibrinogen).[42] The exact mechanism by which NO• suppresses HC protein synthetic function is not known. Preliminary evidence indicates that the NO•-mediated suppression of HC protein synthesis is not dependent on the activation of soluble guanylate cyclase or the inhibition of mitochondrial respiration, but rather that it involves an undefined translational or post-translational regulatory mechanism.[42]

We originally established the KC:HC coculture model as a method to study the role of KC and HC interactions in the changes in liver function associated with sepsis and organ-failure states. Using this model, we demonstrated that multiple cytokines, produced by activated KCs, induce the conversion of L-arginine to NO• within HC, which, in turn, leads to the inhibition of HC total-protein synthesis. The biologic significance of this NO•-mediated inhibition of protein synthesis remains to be determined. *In vivo* experiments suggest that the increased NO• production seen in endotoxemia[22] may protect the liver from damage. In an *in vivo* model of endotoxin-induced hepatic necrosis, the administration of NMA with the endotoxin inhibited nitrogen oxide synthesis while it markedly increased the degree of hepatic damage.[43] The mechanism of the protective action of NO• in the liver and the *in vivo* relevance of the NO•-induced decrease in HC protein synthesis *in vitro* are under investigation.

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DISCUSSION

DR. DOUGLAS WILMORE (Boston, Massachusetts): We have advanced in our knowledge about the metabolic response to injury and sepsis during the last 5 years or so. There are three basic, broad categories of substances that initiate response. One is the catabolic hormones, the second is the cytokines, and the third is the lipid mediators. Several years ago, we presented to this Association evidence that a combination of catabolic hormones could elicit a number of responses to mimic the systemic metabolic responses to injury and sepsis.

This afternoon we heard a very similar type of presentation. However the authors demonstrate that a combination of cytokines can synergistically interact to cause catabolic signals within the hepatocyte.

Is this really cell signaling, or is this cell injury? Are you describing an early response of cell injury that could progress to cell death? Is this similar to the generation of a free oxygen radical that can progress to cause dysfunction of the cell?

The second question has to do with the acute-phase response. Cytokines can initiate synthesis of protein within the liver, which is secreted into the blood stream. Yet your data demonstrate a decreased hepatic protein synthesis. Is this decrease in protein synthesis reflective in secretory proteins or is this simply a decrease in protein synthesis within the cellular matrix of the hepatocyte?

Third, I would like you to speculate on whether these mechanisms that have been elucidated *in vitro* are offered *in vivo*. Do you have data that show that these mechanisms are operative in the whole organism or the whole animal?

Finally, do you have evidence to suggest that the addition of argenine may, in fact, accelerate this pathway and may be deleterious under some conditions, such as sepsis?

DR. WESLEY ALEXANDER (Cincinnati, Ohio): This particular study demonstrates the extreme complexity of the cellular responses in the liver to regulatory factors and emphasizes the need for caution in interpreting *in vitro* effects of individual cytokines. Cytokines may have autocrine-, paracrine-, and endocrinelike functions on cells feeding inhibitory or stimulatory signals to the cells of origin, adjacent cells, or distant cells, which further complicates the interpretation of *in vitro* studies of systems in which effects are concentration dependent, both singly and in combination.

To help clarify the studies, would the authors put in perspective the concentrations of the cytokines used in relationship to the physiologic concentrations *in vivo* in states of health and disease?

As has already been mentioned, arginine has been shown to be a nutrient with pharmacologic effects. In studies by Barbul, Madden, Daly, ourselves, and several others, arginine in concentrations of 1% to 5% of total energy intake have been shown to increase resistance to infection, suppress cancer growth, improve immunologic responses, improve wound healing, and improve survival under certain circumstances.

Because arginine is a substrate for nitric oxide, nitrate, and nitrate in these studies, do you have any evidence that dietary argenine is, in any way, harmful or perhaps, as suggested by another study of yours, is it beneficial because of increased cell mediated toxicity or perhaps even protection of the hepatocyte? Other studies have shown that lipids have a profound influence on cytokine production. Have you any information on how lipids influence cytokine production and nitric oxide production in your system?

The authors and Dr. Simmons' laboratory are to be congratulated for yet another outstanding contribution to paving the pathway for understanding the response of the liver to septic stimuli and ultimately for understanding the mechanisms for hepatic damage and failure.

DR. JONATHAN MEAKINS (Montreal, Canada): In recent times we have been thinking that LPS was not actively the mediator of these injuries but was an initiator, a stimulator of mediators, either cytokines or other molecules, that might be acting as messengers.

The synergistic group of molecules that produce the greatest damage suggests an additional LPS-specific receptor such that LPS has activity without going through a mediator. In this particular setting, does LPS function independently, or does it, indeed, produce some other cytokines or mediators of which we may not be aware?

DR. JOHN H. SIEGEL (Baltimore, Maryland): This is certainly an elegant paper in terms of examining the interactions between various cytokines, but the question I have is related to the end product of these interactions, and that is the hepatocyte synthesized acute-phase protein (APP).

What has been noticed by a number of observers is that in the septic process, the earliest APP response is that of C-reactive protein (CRP) and that initially there is a rise in a wide range of acute-phase proteins, but as the septic process proceeds, there is APP reprioritization with CRP and alpha-1 antitrypsin and fibrinogen remaining high, but transferrin tends to drop off. I wonder whether you have been able to relate the specific types and quantities of proteins that are produced to any of these specific interactions between the various types of cytokines?

DR. J. MINTON (Columbus, Ohio): It was a delightful paper. My question deals with the surgical management of patients who have tumors excised from the liver. We see in the postoperative period a significant drop in their serum protein, especially their serum albumin.

If you add serum albumin to your culture media, does it have any effect on the metabolite production? Will it change one of the mechanisms to prevent breakdown?

DR. BASIL A. PRUITT, JR. (Fort Sam Houston, Texas): In follow-up to one of Dr. Wilmore's questions, I wonder whether you have duplicated this in a system to which activated white cells have been added? I ask that question to raise the heretical possibility that because the oxygen in nitric oxide is the doublet form, as is that in superoxide, if there were cells present that produced superoxide, there could be doublet–doublet annihilation? If such did occur, then superoxide would have a protective role as well as a deleterious role.

DR. JOHN BORDER (Buffalo, New York): I would like to comment on this paper because I think he said his presentation was unique. I would suggest to all of you that what we see here is a generalized phenomenon, that we have activation of the leukocyte systems with release of multiple cytokines, and a very complex regulation by multiple cytokines of practically every phenomenon that they influence.

The essence of the sick person is activation of the leukocyte systems. Because of the complexity of regulation, it is highly unlikely that we will be able to modify this very much by trying to regulate one of the cytokines, but if we turn the problem around and say; How are the leukocyte systems activated, and how do we control activation of the leukocyte systems? we are now looking at something that might have considerable therapeutic possibility, and of course, that is the role of endotoxin and bacteria coming through the gut wall into the portal venous circulation.

Clearly it must be a dominant mechanism that produces illness, but the general question concerns how to reduce activation of the leukocyte systems.

DR. RONALD D. CURRAN (Closing discussion): I would like to answer some of the questions together. First Dr. Wilmore brought up the point whether nitric oxide acts as a signaling mechanism within the cell or just as a toxic molecule such as an oxygen radical. We believe that nitric oxide not only has important actions within the cell as a second messenger, but also functions as an intercellular signal. For example endothelial derived relaxing factor, which is now known to be nitric oxide, is important in mediating vascular tone. Similarly we believe that hepatocyte-derived nitric oxide may play an important role in maintaining blood flow through the hepatic sinusoid specifically by preventing thrombosis. In addition nitric oxide can detoxify oxygen radicals, and may function to protect the hepatocyte from poisons within the portal circulation.

To further investigate the effects of hepatocyte-derived nitric oxide on hepatic metabolism, we developed an *in vivo* model of hepatocyte nitric oxide production. We have found, like others, that a single injection of intravenous or intraperitoneal endotoxin causes a transient increase in serum nitric oxide levels. It is also known that the later induces on increase in interleukin 1 and interleukin 6; however this occurs after nitric oxide production has already peaked. Furthermore we have shown that this endotoxin induced elevation in serum nitric oxide is not from the hepatocyte. To stimulate the hepatocyte nitric oxide synthase enzyme, a more complex and chronic inflammatory state is required. We have shown that a single injection of a small dose of Corynebacterium parvum induces, over a period of 7 days, hepatocyte nitric oxide synthesis. This treatment results in tremendous increases in the serum nitric oxide level, and by harvesting hepatocytes we have shown that the hepatocyte is the source of this increase in nitric oxide. Following injection of *C. parvum* we have isolated the hepatocyte nitric oxide synthase enzyme in the cytosol of the hepatocyte.

What effect does hepatocyte-derived nitric oxide have on liver metabolism? Using this model we have shown that a small injection of endotoxin several days after the *C. parvum* stimulation results in massive hepatic necrosis. If we administer N^G-monomethyl-L-arginine (NMA), the nitric oxide inhibitor, with the endotoxin, the hepatic necrosis is increased. By blocking nitric oxide production with NMA, we promoted liver damage. This suggests that while nitric oxide inhibits hepatocyte total protein synthesis *in vitro, in vivo* hepatocyte-derived nitric oxide functions to protect the cell. Whether this represents a direct nitric oxide-induced alteration in hepatic metabolism or is secondary to maintaining blood flow through the sinusoid is yet to be determined.

In response to Dr. Wilmore's question concerning how the nitric oxide-induced changes in total protein synthesis relate to the hepatic acute-phase response, we believe there are inflammatory conditions in which both the acute-phase response and the nitric oxide-generating pathway are functional in hepatocytes. Similar signals, cytokines, are responsible for inducing these separate hepatic responses and we believe there is most likely some interaction between these two pathways. We have shown that the production of one specific protein of the acute-phase response, fibrinogen, is inhibited by nitric oxide. Interleukin 6 stimulates maximal production of fibrinogen while adding the cytokine signals, which induce nitric oxide production to hepatocytes with interleukin 6, causes an inhibition of fibrinogen synthesis. Furthermore interactions between the acute-phase response and the nitric oxide-generating pathway are under investigation.

As for the role of arginine supplementation in enteral diets, it is known that there are a number of metabolic requirements for arginine, more than just for nitric oxide-generating pathway. *In vitro* studies have shown that arginine supplementation is beneficial for lymphocyte responses, and as Dr. Alexander has noted, there are also *in vivo* data to suggest that arginine dietary supplementation is also beneficial for fighting infections and inhibiting tumor metastases. What role nitric oxide plays in these responses and specifically whether hepatocyte nitric oxide production is involved is unknown. We originally thought that this nitric oxide pathway was completely deleterious to the liver and body in general. However now we believe that the cell's ability to convert arginine to nitric oxide is probably a beneficial response, especially in inflammatory states such as sepsis.

As for Dr. Alexander's question concerning the effects of lipid on the hepatocyte nitric oxide pathway, we have no data to suggest that the lipid composition of the cell membrane has any effect on nitric oxide production.

Dr. Meakins noted that LPS stimulation of hepatocyte nitric oxide production may actually involve an intermediate such as another cytokine. We haven't been able to isolate an indirect effect, although it is possible that the LPS is working through the production of another cytokine. Recently it was shown that hepatocytes possess receptors for endotoxin, suggesting that they probably are able to directly respond to this complex molecule.

Dr. Minton asked whether albumin had any effect on hepatocyte nitric oxide production. Again, as with lipids, we have no data to suggest that the albumin production by the hepatocyte has any regulatory effect on hepatocyte nitric oxide production. Conversely we have shown that nitric oxide inhibits albumin production through a translational or more likely a post-translational mechanism.

Finally Dr. Border commented that the essential question remains: under what circumstances are we going to control or inhibit these leukocyte responses, the cytokine production, and now the nitric oxide production as well? That mystery remains to be solved. The nitric oxide pathway itself downregulates macrophage function, specifically through inhibiting complex I and complex II of the electron transport chain and the Kreb's cycle enzyme aconitase. Therefore nitric oxide production by a number of different cell types may act in concert to cause the downregulation of the immune response. It may be or represent a negative feedback response to control the production of cytokines and detoxify oxygen radicals.

Experience with Cardiopulmonary Bypass and Deep Hypothermic Circulatory Arrest in the Management of Retroperitoneal Tumors with Large Vena Caval Thrombi

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From June 1984 to September 1989, 43 patients with large vena caval tumor thrombi from retroperitoneal malignancies underwent surgical treatment with cardiopulmonary bypass (CPB) and deep hypothermic circulatory arrest (DHCA). The primary malignancies were renal cell carcinoma (RCC) (n = 39), renal pelvic transitional cell carcinoma (n = 1), adrenal pheochromocytoma (n = 1), and renal (n = 1) or retroperitoneal (n = 1) sarcoma. The level of the caval thrombus was either suprahepatic (n = 27), intrahepatic (n = 14), or subhepatic (n = 2). In all cases the primary tumor and caval thrombus were completely removed. Concomitant procedures included coronary artery bypass grafting (n = 5), pulmonary resection (n = 2), and hepatic lobectomy (n = 1). The time of circulatory arrest ranged from 10 to 44 minutes (mean, 23.5 minutes). There were two operative deaths (4.7%), neither of them due to to the use of DHCA. Major postoperative complications occurred in 13 patients (30.2%). There were no ischemic or neurologic complications and no cases of perioperative tumor embolization. The median postoperative hospital stay was 9 days. Twenty-two patients (51%) are alive and enjoying a good quality of life. The 3-year patient survival rates in patients with localized (n = 24) *versus* metastatic (n = 15) RCC are 63.9% and 10.9%, respectively (p = 0.02). We conclude that CPB with DHCA facilitates excision of retroperitoneal malignancies with large caval thrombi and provides the potential for cure with low morbidity and mortality rates.

CARDIOPULMONARY BYPASS (CPB) with deep hypothermic circulatory arrest (DHCA) recently was established as a useful adjunct in the surgical management of patients with renal cell carcinoma (RCC) and large inferior vena caval (IVC) tumor thrombi.[1] This approach requires close collaboration between a urologic and cardiac surgical team. At our center, CPB with DHCA is the preferred technique for patients undergoing removal of nonmetastatic RCC and an intrahepatic or suprahepatic IVC thrombi. We also have used this approach in selected patients with other types of retroperitoneal malignancy associated with a large IVC thrombus.

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We present here our experience with CPB and DHCA in the management of 43 patients with retroperitoneal tumors and large caval thrombi. The intent of this review is to clarify the selection and evaluation of patient candidates as well as the operative morbidity and clinical outcome with CPB and DHCA in this setting.

Materials and Methods

From June 1984 to September 1989, 43 patients with retroperitoneal malignancies and associated IVC tumor thrombi underwent surgical treatment using CPB and DHCA. This series includes 28 men and 15 women ranging in age from 33 to 81 years (mean age, 62.5 years). The primary malignancy was RCC in 39 patients, renal pelvic transitional cell carcinoma in 1 patient, malignant fibrous histiocytoma in 1 patient, adrenal pheochromocytoma in 1 patient, and retroperitoneal leiomyosarcoma in 1 patient. The primary tumor was on the right side in 30 patients, on the left side in 12 patients, and in the midline in 1 patient. The distal level of the vena caval tumor thrombus was below the most inferior hepatic vein (subhepatic) in 2 patients, within the intrahepatic portion of the IVC in 14 patients, and above the most superior hepatic vein (suprahepatic) in 27 patients; the latter category includes 10 patients whose thrombi extended to the intrapericardial portion of the IVC and 17 patients whose thrombi extended into the right atrium.

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The preoperative evaluation included a chest x-ray, abdominal computerized tomography scan, renal arteriography, and either inferior vena cavography or magnetic resonance imaging of the IVC. Right heart catheterization with injection of the superior aspect of the IVC was done if there was IVC occlusion or if magnetic resonance imaging did not clearly demonstrate the distal extent of the thrombus. Coronary arteriography was obtained routinely and echocardiography was done selectively to define tumor extent. Renal arterial embolization was performed 48 to 72 hours before surgery in eight patients with evidence of a hypervascular IVC tumor thrombus on renal arteriography.

Nine patients with RCC had evidence of distant metastatic disease before operation. There was no evidence of metastasis in the four patients with non-RCC malignancies. The patient with an adrenal pheochromocytoma was known to have direct tumor extension into the liver.

The hospital charts of all patients were reviewed and follow-up information was obtained through direct contact with either the patient or his or her local physician. Complete follow-up data are available for all patients. The follow-up interval ranges from 6 to 67 months, with a mean of 22 months. Patient survival estimates were calculated using the Kaplan–Meier method with statistical comparisons by the log-rank test.

Results

Operative Technique

The anesthetic considerations for CPB with DHCA are described in detail elsewhere.[2] The surgical technique followed previously described methods.[3] Briefly, a lateral subcostal abdominal incision is made and the retroperitoneal tumor mass is mobilized. In cases of RCC, the entire kidney is mobilized and left attached only by the main renal vein with the tumor thrombus. After maximum mobilization of the tumor, a median sternotomy is performed, the patient is heparinized, and the aorta and right atrium are cannulated. Cardiopulmonary bypass is instituted with systemic cooling. This is augmented by the use of topical cold solution in the abdomen and chest. After a core temperature of 18 to 20 C has been achieved, cardiopulmonary bypass is terminated and the blood volume is drained into the pump. The vena caval tumor thrombus then is removed in a bloodless operative field. After extraction of the thrombus and repair of the caval wall, cardiopulmonary bypass is reinstituted and the patient is rewarmed to a core temperature of 37 C. Cardiopulmonary bypass is terminated and heparin is reversed.

In all cases the primary malignancy and IVC tumor thrombus were completely removed. An atriotomy was done in all patients with tumor thrombus extending into the right atrium and in selected other patients with friable or adherent thrombi. One patient underwent vena caval reconstruction with a pericardial graft. Additional procedures done at the time of CPB with DHCA included coronary artery bypass grafting in five patients, pulmonary resection of metastases in two patients with RCC, and hepatic lobectomy in the patient with an invasive adrenal pheochromocytoma.

The circulatory arrest time in this series ranged from 10 to 44 minutes, with a mean of 23.5 minutes. The number of perioperative blood transfusions administered per patient ranged from 3 to 56 units, with a median of 9 units. The postoperative hospital stay ranged from 7 to 76 days, with a median of 9 days.

Operative Mortality and Morbidity Rates

Two patients died within 30 days of surgery, for an operative mortality rate of 4.7%. One patient died of an adverse reaction to protamine given to reverse heparinization at the completion of an otherwise technically successful operation. The second operative death occurred in a critically ill 79-year-old man with Budd–Chiari syndrome and severe noncorrectable coronary artery disease. This patient experienced an intraoperative myocardial infarction and could not be weaned from CPB, despite multiple attempts.

Major postoperative complications occurred in 13 patients (30.2%). These patients experienced a total of 18 complications, as listed in Table 1. Three patients underwent repeat surgical exploration for retroperitoneal hemorrhage on the first postoperative day. One patient required immediate reoperation for mediastinal bleeding from a coronary artery bypass graft. All of the remaining complications resolved with appropriate treatment. Temporary acute renal failure occurred in one patient who did not require dialysis. There were no other ischemic or neurologic complications. There were no cases of perioperative tumor embolization.

TABLE 1. *Postoperative Complications After Cardiopulmonary Bypass with Deep Hypothermic Circulatory Arrest in 13 Patients*

Complication	Number of Occurrences
Retroperitoneal hemorrhage	3
UGI bleeding	3
Deep vein thrombosis	3
Wound infection	2
Pneumonia	2
Cecal volvulus	1
Pancreatitis	1
Acute renal failure	1
Adrenal insufficiency	1
Mediastinal hemorrhage	1

UGI, upper gastrointestinal.

Pathologic Findings

Of the 39 patients with RCC and an IVC tumor thrombi, the renal parenchymal tumor was contained within Gerota's fascia in 24 patients; there was no capsular penetration in 19 patients, while 5 patients had perinephric fat involvement. Six patients had regional lymph node involvement with no distant metastasis. Distant metastatic disease was present in nine patients.

The four patients with non-RCC malignancies underwent complete surgical excision of all gross tumor. The patient with a renal pelvic transitional cell carcinoma had a grade II tumor with regional lymph node involvement. The patient with an adrenal pheochromocytoma underwent *en bloc* resection of the primary tumor and a contiguous lobe of the liver. In the patient with a leiomyosarcoma, the tumor originated from the posterior wall of the IVC and was completely excised. In the patient with a malignant fibrous histiocytoma, there was direct invasion of the IVC wall that was resected.

Patient Survival

Among the group of 39 patients with RCC, 19 patients (48.7%) are alive with follow-up ranging from 6 to 67 months. Among these survivors, the follow-up interval is more than 2 years in 8 patients (mean, 39.1 months), 1 to 2 years in 4 patients (mean, 17.5 months), and less than 1 year in 7 patients.

Among all patients with RCC, the 1-, 2-, and 3-year actuarial survival rates are 61.3%, 49.0%, and 32.2%, respectively. The 3-year survival rate for patients with localized RCC (within Gerota's fascia) is 63.9%, compared to 10.9% for patients with either lymph node or distant metastases (p = 0.02) (Fig. 1). Among patients with localized RCC, there was no significant difference in survival rates between those with or without perinephric fat involvement (p = 0.16). There was no significant difference in survival between patients with lymph node metastasis only compared to those with distant metastasis (p = 0.46).

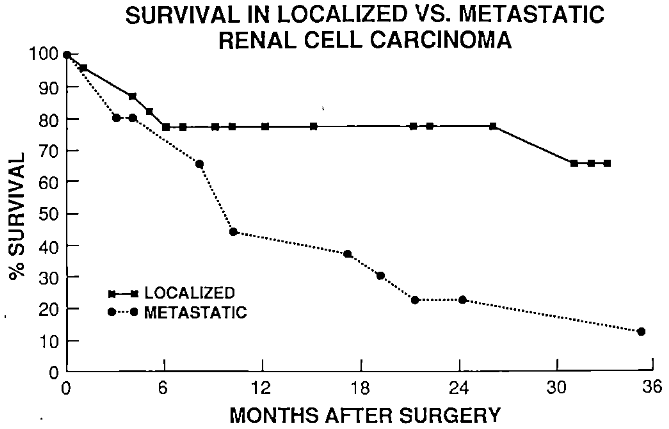

FIG. 1. Actuarial patient survival in patients with localized (n = 24) *versus* metastatic (n = 15) RCC after CPB with DHCA.

TABLE 2. *Location of Inferior Vena Caval Tumor Thrombi in Patients with Localized* Versus *Metastatic RCC*

	Intrahepatic Thrombus	Intrapericardial Thrombus	Intra-atrial Thrombus
Localized RCC (n = 22)	7	3	12
Metastatic RCC (n = 15)	8	5	2

p = 0.04.
RCC, renal cell carcinoma.

Table 2 demonstrates the distribution of intrahepatic, intrapericardial, and intra-atrial IVC tumor thrombi among RCC patients with localized *versus* metastatic disease. There was no positive correlation between the presence of metastasis and more distally propagating tumor thrombi. In fact a significantly greater proportion of intra-atrial thrombi were observed in patients with localized RCC compared to those with metastatic RCC (p = 0.04). The 3-year survival rate for patients with intra-atrial thrombi (56%) was better than that for patients with intrapericardial (0%) or intra-hepatic (41%) thrombi; however these differences are not statistically significant (p = 0.21).

Three of the four patients with nonrenal malignancies are currently alive and free of tumor. The patients with leiomyosarcoma, pheochromocytoma, and renal pelvic transitional cell carcinoma are alive at 13, 13, and 28 months, respectively. The patient with malignant fibrous histiocytoma died 34 months after operation of metastatic disease.

Discussion

The most common retroperitoneal tumor associated with an inferior vena caval thrombus is renal cell carcinoma. Approximately 20,000 new cases of RCC are discovered annually in the United States and the incidence of IVC involvement is 5%.[4] Other less common tumors that can present with a caval thrombus include Wilm's tumor, renal pelvic transitional cell carcinoma, renal or retroperitoneal sarcoma, adrenal cortical carcinoma, pheochromocytoma, and lymphoma. In such cases, an aggressive treatment approach is warranted if the tumor is localized and complete surgical removal can be accomplished.

For patients with nonmetastatic RCC and IVC involvement, 5-year survival rates of 47% to 68% have been reported following complete surgical excision.[5-7] The presence of lymph node or distant metastases in such cases carries a dismal prognosis that is not appreciably altered by radical surgical extirpation.[8] There is a palliative role for surgery in some patients with metastasis who experience severe disability from intractable edema, ascites, cardiac dysfunction, or associated local symptoms such as abdominal pain or hematuria. Some biologic-response modifier (BRM) protocols to treat patients with metastatic RCC also require preliminary removal of the primary tumor. In the present series, 24 of 39 patients with RCC had localized tumors that were removed completely. The remaining 15 patients with nodal or distant metastasis underwent surgery for palliation of severe symptoms from the primary tumor and caval thrombus or to allow entry into a BRM treatment protocol.

Accurate preoperative information regarding the presence and complete extent of an IVC tumor thrombus is essential to determine the appropriate operative approach. Computed tomographic scanning and ultrasound usually will detect gross renal vein and IVC involvement but are unreliable in delineating the cephalad extent of a thrombus. Inferior vena cavography has been the most accurate diagnostic study for assessment of IVC thrombi; however a single antegrade study may be insufficient with complete caval occlusion; in such cases a second retrograde injection of the IVC is needed to define the distal limits of the thrombus. Recent data indicate that magnetic resonance imaging (MRI) is an accurate noninvasive method for delineating the full extent of IVC thrombi,[9,10] and now this is the preferred caval imaging modality at our center. Inferior vena cavography is reserved for patients in whom MRI findings are equivocal or when MRI is contraindicated, as in patients with claustrophobia, cardiac pacemakers, certain intracerebral vascular clips, cochlear implants, or intraoccular foreign bodies.

We continue to perform renal arteriography before operation in patients with RCC and an IVC thrombi. Large caval thrombi often demonstrate hypervascularity with distinct arterial supply from the renal artery. When this finding is observed on arteriography, we perform renal arterial embolization 2 to 3 days before surgery. We have observed several cases of definite shrinkage in the size of a caval thrombus following such embolization, which has facilitated its intraoperative removal. This practice was followed in eight patients from the present series with intraoperative benefit and no unusual sequelae.

The preoperative cardiac evaluation of patients considered for CPB with DHCA should include coronary arteriography and left ventriculography. This is helpful not only to better define the risk of surgery but also to identify significant correctable coronary artery lesions in an age group in which such lesions are common. These lesions can be repaired during cooling or rewarming without extending the total operative time. This was done safely in five patients from the present series and has been reported by others.[11] Cardiac echocardiography is useful to assess the presence of thrombus in the right atrium but is now obtained only if an MRI study is equivocal.

In performing surgical removal of an IVC thrombus, it is essential to obtain control of the cava above the thrombus to prevent intraoperative embolization of a tumor fragment. Temporary occlusion of the infrahepatic IVC can be safely done, but occlusion of the suprahepatic IVC often causes a profound decrease in venous return with hypotension; additional disadvantages of the latter maneuver when removing a caval thrombus include backbleeding from hepatic and lumbar veins and occasional swelling of the liver from venous congestion, which interferes with exposure. Several techniques have been used to remove large caval thrombi when distal caval control cannot be achieved below the liver. These include cross-clampling of the supraceliac aorta,[12] occlusion of the intra-pericardial vena cava with simultaneous occlusion of the porta hepatis and superior mesenteric artery,[7] use of an intraoperative venous (caval-atrial) shunt,[13,14] and cardiopulmonary bypass alone.[15]

Cardiopulmonary bypass with deep hypothermic circulatory arrest offers several advantages over the above techniques. Because formal isolation and control of the distal IVC is not necessary, extensive retrohepatic or intrapericardial caval dissection is avoided. There is no need for occlusion of the porta hepatis, ligation of multiple lumbar veins, or aortic cross-clamping to prevent hemorrhage. Cardiopulmonary bypass with DHCA allows direct visual inspection of the entire vena caval lumen in a completely bloodless field. An atriotomy can be performed easily, which facilitates removal of not only atrial thrombus but also friable or adherent pieces of thrombus in the intrahepatic IVC. The risk of sudden massive intraoperative hemorrhage or distal tumor thrombus embolization is lessened. Finally DHCA allows up to 60 minutes of safe ischemia in a bloodless field for the performance of vena caval thrombectomy or resection and appropriate caval reconstruction. The maximum period of safe ischemia with occlusion of the suprahepatic IVC and porta hepatis is only 20 minutes.

The data in this series indicate that DHCA is a safe and effective approach. The operative mortality rate was 4.7% and neither of the two patient deaths were due to the use of DHCA. Other recent reports have indicated operative mortality rates of 4.5%,[5] 9.3%,[6] and 13%[7] after surgical removal of RCC with IVC involvement. The incidence of major postoperative complications in our series also was not excessive considering the magnitude of the surgical problem and the critically ill nature of many patients.

The most common postoperative complication was hemorrhage requiring surgical re-exploration, which occurred in four patients. Cardiopulmonary bypass is associated with temporary platelet dysfunction[16] and this effect may be augmented with superimposed DHCA. While this issue requires further study, bleeding was not a problem for most patients. The median total number of perioperative blood transfusions per patient was nine units, which compares favorably to blood replacement data with other techniques. In a recent report of 53 patients treated surgically for RCC with IVC involvement, with CPB used in only three patients, the mean intraoperative blood replacement per patient was 10 units.[7] These observations notwithstanding, persistent bleeding after CPB is a potential problem that requires prompt and aggressive management. We have treated this problem with platelets, fresh-frozen plasma, desmopressin acetate, aminocaproic acid, or a combination of these. Recent data suggest that high-dose aprotinin has a dramatic ability to normalize coagulation after CPB and reduce transfusion requirements.[17] We are now incorporating this into our regimen.

The 3-year survival rate following surgical excision of nonmetastatic RCC with an IVC thrombus was 63.9%, which supports aggressive treatment in this setting. It has been suggested that the risk of metastasis and early death in RCC is increased with suprahepatic thrombi compared to intrahepatic thrombi.[18] This observation was not borne out in the present series, in which intra-atrial thrombi were associated with neither an increased risk of metastasis nor compromised patient survival.

We believe that CPB with DHCA is the preferred procedure for patients with an intrahepatic or suprahepatic IVC thrombus from retroperitoneal malignancy. This approach is safe, effective, and allows extensive IVC thrombi to be completely removed with excellent exposure in a controlled operative setting.

The success of DHCA during CPB for a complicated surgical procedure raises the possibility of this type of support for other noncardiac procedures that are potentially hazardous due to the risk of hemorrhagic complications or cardiovascular catastrophe. The use of CPB generally has been avoided because of the associated coagulopathy and the difficulty with vascular access. Experience with cardiac procedures using aprotinin suggests that the former problem can be vastly reduced or eliminated by the use of this drug. The development and commercial availability of arterial and venous cannulae that can be inserted in the femoral vessels percutaneously and can maintain cardiopulmonary support may solve the latter problem. With these two new adjuncts, it will be appropriate to re-evaluate the use of DHCA in other settings, such as complex aortic surgery, hepatic transplantation, intracranial aneurysm repair, and resuscitation from multiple trauma.

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DISCUSSION

DR. EDWARD J. BEATTIE (New York, New York): We also agree that most of these are kidney cancers and most of the time the tumor has not gotten into the atrium, as the author showed.

There is no question that when the tumor is in the atrium that the bypass technique is mandatory and must be done. However, during the last 12 years at Memorial Sloan-Kettering in New York, our thoracic service, working with Dr. Whitmore's urology service, has had 25 of these patients with extensive tumor thrombi in the upper abdominal inferior vena cava. Of course it all depends on whether the kidney itself is removed, as has already been indicated, and Dr. Mangit Bains has developed a somewhat different technique that I would like to call to your attention because I think it also works very well.

It has the advantage that you do not have to heparinize the patient. It also has the advantage that all the fragments extend in the correct direction, which means away from the heart. After one has dissected out the kidney, one places a tape on the inferior vena cava, just below the heart above the liver, and then places additional tapes on the inferior vena cava below the renal vein, above the renal vein and on the good renal vein. As one pulls up on the tape just below the heart, there is a marked rise in pressure in the inferior vena cava from the hepatic flow, and with all the other tapes closed, except for the kidney, to come out, one can cut the renal vein for removal. One then has a gush of blood with retrograde delivery of the tumor. Let some blood flush out. Our experience has been that one gets all the tumor out this way.

Now one can do preoperative studies, including the CT scan, with contrast angiograms and sonograms. You must be sure that the tumor is not in the heart. You can also try to see that the tumor is not adherent to the inferior vena cava. If it is adherent, it is usually local and one gently frees it.

If it is locally invasive, you can excise it. If it has been bulky, it has already obstructed the cava, and usually there are venous collaterals from the other kidney. If necessary, one can ligate the vena cava at that point, as long as the other kidney has adequate venous drainage.

In the 25 cases that have been done during the last 12 years, there were no deaths from the operation. Bains wanted me to tell you that he had one patient in whom the tumor came from the uterus. It went through the iliac up into the vena cava just below the heart. It was flushed out retrograde *via* the iliac vein.

DR. JAMES F. GLENN (Lexington, Kentucky): Dr. Novick was one of the earliest investigators of bench surgery for renal disease, and here he has essentially reversed his field and rendered the entire operative area the bench. I think he confirms what we have heard previously.

Last year you will remember that Dr. Donald Skinner of Los Angeles presented his results with large renal cell tumors extending into the atrium.

I am reminded that my first experience with this was in 1958 as a resident with Dr. Edwin P. Alyea, who operated on a patient who had a previously undiagnosed thrombus extending into the atrium with a cavotomy, much in the manner that Dr. Beattie has just described. We were able to extract the thrombus. It was the first time I had ever seen this done, and it was the first time that Dr. Alyea had ever seen it done. Remarkably that patient survived for some 30 years.

I followed the patient until leaving Duke in 1980. I think the patient died in 1979, so long-term results of thrombectomy are very heartening.

As we look at this paper, I think the most apparent thing to me is the extrapolation of this technique to other diseases. This series deals largely with renal cell carcinoma, but I see no reason why similar techniques should not be used for other intra-abdominal disease, and particularly in extensive pelvic disease, diseases such as carcinoma of the bladder, which we have deemed inoperable in the past. With such deep hypothermic circulatory arrest and cardiopulmonary bypass, it seems that there is an opportunity here to apply this technology to the removal of extensive pelvic tumors, which thus far have eluded surgical cure.

DR. LAZAR J. GREENFIELD (Ann Arbor, Michigan): We have heard reference to the description of what is in the vena cava as thrombus, whereas I believe it is usually tumor, as we could see from the arteriogram that demonstrated so nicely the presence of an intact blood supply. That is what allows the surgeon to remove the propagating tumor intact.

It is very unusual to have thrombus attached to that portion of the tumor.

We had occasion to be very concerned about the presence in one patient of what appeared to be a fragment of tumor in the pulmonary artery, and treated that particular patient on bypass, but what we extracted was a fragment of thrombus rather than tumor. The fact that the tumor remains intact gives us this option of separating it from the wall of the vena cava because thrombus itself would usually adhere strongly to the vena cava during a period of time and not allow such removal.

We have also approached those tumors that have not propagated up above the level of the hepatic veins by inserting a filter before proceeding with the intra-abdominal portion of the resection. That allows some control over the thrombus that might be attached to the tumor, and I would ask the authors if the histology of what was in the vena cava was actually tumor rather than thrombus.

DR. ANDREW C. NOVICK (Closing discussion): Dr. Beattie has presented an interesting experience using an alternative technique for tumors that do not extend into the right atrium, namely, the approach of occluding the intrapericardial portion of the inferior vena cava.

I was interested to hear the good results obtained with this approach. We have been somewhat reluctant to perform occlusion of the intracardial vena cava without adjunctive occlusion of the porta hepatis and the SMA due to concerns about inducing hypotension, liver engorgement, and bleeding from the hepatic and lumbar tributaries entering the inferior vena cava. However, this appears to be an approach that can work for some tumors that do not extend into the atrium.

In response to Dr. Greenfield's question regarding terminology, let me state very clearly that we are talking about tumor thrombi that extend from the kidney into the vena cava and then distally for a variable distance. In many of these cases, we also find thrombus in the vena cava below the level of the renal vein. This infrarenal thrombus is invariably bland thrombus that does not contain tumor. I appreciate the opportunity to clarify this point.

Dr. Glenn raised what is perhaps the most intriguing issue, namely, other applications of the technique of hypothermic circulatory arrest, which does indeed appear to be safe and without significant ischemic sequelae. My own view is that this has a great deal of potential application to other types of difficult pelvic and retroperitoneal surgery, and I anticipate that its indications will be extended to these areas as well.

I would like to add one comment of my own that I was not able to make in the presentation, and that is concerning the role of surgery in patients with renal cell carcinoma whose tumors are not localized. In our series, we operated on 15 patients with either nodal or distant metastasis, and I would like to emphasize that the indications for doing so were either for palliation of severe associated symptoms from their tumor or as an adjunct to allow entry into a biologic response-modified protocol.

Urinary Tract Refunctionalization After Long-term Diversion

A 20-year Experience with 177 Patients

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From 1969 to 1990, previously diverted urinary tracts were 'undiverted' in 177 patients whose ages ranged from 1 to 31 years. Fifty-six of the patients (32%) had been diverted for 10 years or longer. There were 67 female and 110 male patients. Forty-four patients had only one kidney and in two of those patients it was a previous renal transplant. One patient was anephric at the time of reconstruction, having had two unsuccessful transplants. Most of the diversions had been considered permanent. Types of diversions that were reversed included ileal loop, colon conduit, loop ureterostomy or pyelostomy, end ureterostomy, cystostomy or vesicostomy, long-term nephrostomy, and ureterosigmoidostomy.

SIXTEEN YEARS AGO an initial experience was reported in refunctionalization of the urinary tract after previous diversion (undiversion) in 32 children.[1] Since then the indications for undiversion have broadened considerably. They now include some patients with neurogenic bladder[2,3] and many patients with a small, noncompliant, scarred bladder who were formerly considered poor candidates for undiversion. It is clear also that undiversion can be done for some adults who have had diversions for many years.[4] Key factors in the wider use of undiversion include (1) augmentation cystoplasty,[5-13] (2) the ability to construct a female urethra from vaginal wall and a buttocks flap,[14] (3) improved bladder neck reconstruction, and (4) use of intermittent self catheterization[15] in those patients who cannot void spontaneously after the bladder outlet is narrowed to increase outlet resistance and the bladder is augmented to increase its volume and compliance.

This report will summarize an experience with 177 undiversion operations in children and young adults. Each case is unique, differing in some respects from most others. However there are certain general surgical principles that are common to all of these reconstructions. They will be emphasized. Illustrative cases will be shown to demonstrate the wide spectrum of patients who can be undiverted. The reasons for original diversions were varied. They included (1) neurogenic bladder; (2) severe hydronephrosis in boys with urethral valves; (3) failed ureteral reimplantation surgery for vesicoureteral reflux; (4) failed surgery to correct congenital incontinence from various malformations such as exstrophy, epispadias, ureteroceles, and bilateral single ectopic ureters; (5) prune belly syndrome; (6) complex anomalies, such as cloacal malformations, that were considered irreparable; (7) cancer; (8) trauma; and (9) contracted bladder after chemotherapy and radiation therapy.

Patients and Methods

The ages of the patients shown in Figure 1 ranged from 1 to 31 years. The duration of the various urinary diversions, shown in Figure 2, ranged from 1 to 27 years. In 56 cases (32% of the series), the urinary diversion had been present for 10 years or longer.

Figure 3 lists the types of urinary diversions that had been done previously in these patients. Sixty-six had ileal conduits, of which 14 were pyeloileal conduits, *i.e.*, there were no ureters with which to reconstruct the patient. Thirteen patients had nonrefluxing colon conduits, some of which had been done with a view to ultimately reconstruct the lower urinary tract. In three of those patients there had been originally an ileal loop with reflux and deterioration of the upper tracts. Loop ureterostomy or pyelostomy was present in 39 patients. Seventeen patients had end ureterostomy or vesicostomy. Seven had long-term nephrostomy drainage, and one had ureterosig-

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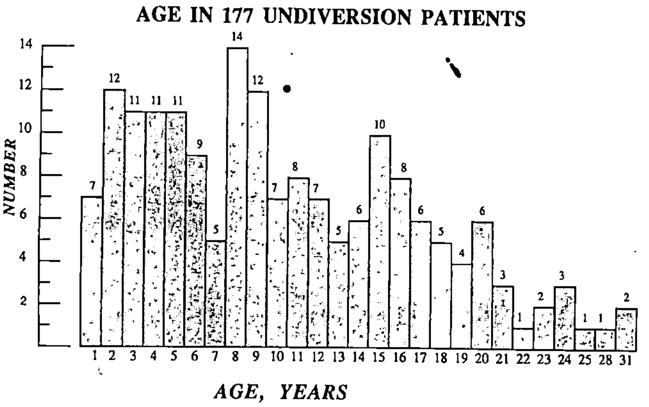


FIG 1. Age in 177 undiversion patients.

URINARY UNDIVERSION

1969 - 1990 177 CASES

66	ILEAL LOOP (14 pyelo-ileal)	126	permanent diversions
13	COLON CONDUIT (3 had been ileal loops)	51	temporary diversions
39	LOOP URETEROSTOMY or PYELOSTOMY	67 110	females males
17	END URETEROSTOMY	44	pts. had one kidney (2 a transplant)
34	CYSTOSTOMY or VESICOSTOMY	1	patient anephric (later transplanted)
7	NEPHROSTOMY		
1	URETEROSIGMOIDOSTOMIES		

12 personal diversions; 165 had been diverted elsewhere

FIG 3. Data on 177 undiversion cases.

moidostomies that required change because of deteriorating upper tracts and urinary incontinence by rectum. Of the 177 cases, 12 of the diversions had been performed many years earlier by the author, and 165 had been diverted elsewhere; 126 had been thought to be permanent urinary diversions; in 51 the diversion had been done as a temporizing procedure, usually in an infant to relieve severe hydronephrosis with the aim of ultimately repairing its cause at a later age. Most such patients today would be treated by an early reconstructive procedure during infancy.[16,17] There were 67 female and 110 male patients. Forty-four patients had only one kidney each; in two this was a transplanted kidney. One patient was referred on chronic hemodialysis after multiple reconstructive operations and two failed cadaver renal homografts. The bladder was reconstructed by augmenting it with cecum, and a living related renal transplant was performed later with success.

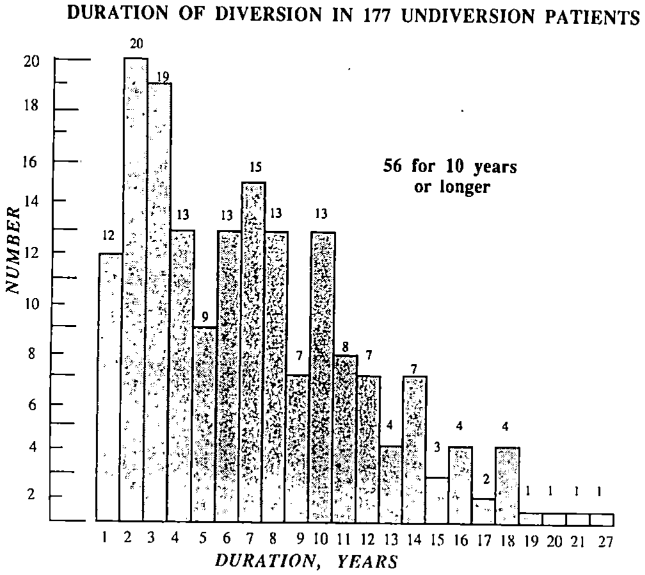


FIG 2. Duration of diversion in 177 undiversion patients.

Preoperative evaluation was as complete as possible in all patients and included the following. (1) Upper tract visualization by intravenous pyelography or by retrograde filling through a diversion stoma. (2) Radionuclide scan to assess the relative function of the two kidneys, with a drainage catheter present if there was an anatomic situation that would allow reflux from one kidney to another. When one kidney is atrophic, and total renal function is satisfactory, it may be best to remove a kidney that contributes less than 10% of the patient's function. (3) Cystogram examination to evaluate the bladder, urethra, and ureteral stumps. Some long diverted bladders become small with disuse, but others do not and maintain good volume. It is important to know why the patient was diverted originally. For example, if the problem was wetting secondary to neurogenic bladder caused by myelomeningocele, the same problem will persist. On the other hand, if the patient's diversion was performed after multiple failures of ureteral reimplantation, the patient's continence mechanism of the bladder neck and external sphincter may be normal. (4) Urodynamic assessment can demonstrate bladder size, sensation, compliance, outlet resistance, sphincter contractility, ability to retain instilled saline, and other parameters.[18] Its value often was limited when the bladder was small and scarred. (5) Cystoscopy was performed before operation on all patients under anesthesia to. assess the anatomy. In patients in whom control had been present originally, a suprapubic catheter was inserted during endoscopy to allow cycling of the bladder with saline,[19,20] to test its ability to increase its size, and assess the patient's ability to empty the bladder. Cycling the bladder was not valuable when there was incontinence. If urethral valves were present, they were not fulgurated while the bladder was defunctioned. This is likely to be followed by scarring and obliteration of the urethral lumen in a 'dry urethra.'[21] It was performed during bladder cycling with saline or later at the time of undiversion, when a catheter would be in place and on its removal the patient would void. (6) Psychological evaluation: It can not always be predicted which patient will be unable to void following an undiversion reconstruction, especially if a procedure is performed to increase outlet resistance and the bladder is augmented. This must be completely understood by the patient, who must be willing to learn self catheterization. (7) Renal function by 24-hour creatinine clearance is measured before operation. If function is poor, long-term collaboration with a nephrologist is essential. Use of bowel in reconstructing the urinary tract when there is poor function may promote solute resorption and loss of fixed base, aggravating the problem of acidosis if appropriate measures are not taken. Poor renal function was not considered a contraindication to undiversion surgery. Many of the patients had poor renal function when undiverted, so it could be predicted that transplantation would be needed in the future, especially during the transition from childhood to adult size. Two of the patients had received a renal transplant, one into an ileal loop and the other into the native bladder with vesicostomy drainage. A third patient had undergone two cadaver transplantations into a colon conduit, both of which were rejected. Anephric and on hemodialysis at the time of referral, the bladder was reconstructed, and later a maternal kidney was joined to the augmented bladder with success. (8) Cultures were obtained before operation to guide administration of antibiotics.

After thorough investigation of the patient's anatomy, renal function, bacteriology, and psychologic preparedness for major surgery, the technical aspects of undiversion must be considered.[22] A thorough bowel preparation was obtained in all patients. In the last 5 years this was done with Golytely (Braintree Laboratories, Braintree, MA). This polyethylene glycol electrolyte gastrointestinal tract lavage solution is a powder that is diluted with tap water and administered orally. It passes rapidly through the gastrointestinal tract, cleaning it well.

Anesthesia included complete monitoring of arterial pressure, venous pressure, hematocrit level, electrolytes, blood gases, and urinary output, which is essential in these often lengthy operations. Fluid replacement was frequently in the range of 15 to 25 mL/kg/hr, far in excess of the rate of 5 mL/kg/hr, which will maintain metabolic homeostasis in many types of surgery.

Operative access was usually through a long vertical midline incision from the symphysis pubis to the xyphoid process of the sternum. When nephrostomy, pyelostomy, or loop ureterostomy was present, the flanks also were prepped and draped for sterile access during operation.

Psoas hitch was used as an adjunct in ureteral reimplantation in many cases. This compensates for lack of length of a ureter and prevents angulation of a reimplanted ureter or tapered bowel segment during filling of the bladder.

Transureteroureterostomy[23] or transureteropyelostomy often was used, implanting the better ureter into the bladder, usually with a psoas hitch, and draining the contralateral side across the abdomen into the reimplanted ureter. Care was taken to avoid wedging the ureter crossing the abdomen beneath a major mesenteric vessel, which can cause obstruction.

Augmentation of the bladder, using small bowel, cecum, sigmoid colon, or stomach was used in 60 of the patients who had small, noncompliant bladders. Etiology of the small bladder included myelodysplasia, scarring from previous operations, urethral valves, exstrophy and epispadias, fibrosis after tumor therapy, trauma, and cloacal malformation.

At least one ureter was reimplanted into the bladder whenever possible. Bridging the gap between the kidney and bladder was done by use of bowel only when satisfactory ureteral reimplantation was not feasible.

Results and Complications

There were no early postoperative deaths, indicating that these global reconstructions can be performed with safety if meticulous attention is paid to avoid ureteral obstruction, anastomotic leakage, and so on. There were 8 late deaths (1 to 14 years after operation), the causes for which were trauma (n = 2), septicemia during hemodialysis (n = 1), massive stroke (n = 1), varicella infection after renal transplantation (n = 1), acute leukemia (n = 1), anaphylactic reaction during intravenous pyelogram examination (n = 1), and failure to take prescribed immunosupressive drugs (n = 1).

Renal transplantation was performed, to date, in 23 patients. These included two patients who had undergone transplantation before undiversion and one patient who was anephric at the time of bladder reconstruction. An additional 40 of the 177 cases probably will require renal transplantation within the coming decade, judging from their original and current renal function values. In no patient did renal function fall unexpectedly after undiversion from an obstruction or other complication. In most patients it was the expected decline in creatinine clearance, which occurs with growth, in which the body weight increases, resulting in relative renal insufficiency. For example our third undiversion patient was reconstructed at age 6 years in 1969. His creatinine clearance was then only 24 L/m^2 of body surface area, about 20% of normal. Renal transplantation was performed 20 years later at age 26 years in 1989. Twenty-three patients required reoperation for persisting reflux. Sites of reflux included the ureter (n = 9), bowel ureter (n = 6), and an ileocecal nipple (n = 8). Longer tunnels were made for the ureters. Longer tunnels were made in three of the bowel ureters, and three were converted to ileocecal conduits. The nipples were revised by sewing them to the cecal wall or substituting a tapered and tunnelled bowel segment. Two patients had perforation of bladder augmentations, one from a karate kick and the other from a spontaneous event. This is a known risk of bladder augmentation.[24,25] Both perforations were successfully closed surgically. Eight patients required reoperation for partial obstruction. These partial obstructions were in the ureter in five and late stricture of a bowel ureter occurred in three, each very localized. An endoscope can be passed up a bowel ureter to (1) incise a web, (2) inject steroid solution, or (3) dilate it. Urinary tract stones developed in 12 patients and required removal. Most of the stones had a staple nidus. When staples have been used, I always cystoscope the patient several months later to remove any staples not covered by mucosa. Otherwise they can form stones on the nipple or drop off into the bladder and grow larger, which occurred in two patients who did not return soon for follow-up examination. Three patients had postoperative leaks and all of them closed spontaneously. Two patients had pigment gallstones on follow-up, presumably from large intraoperative transfusion requirement during undiversion. Cholecystectomy was done in each of these patients. One patient had a traumatic urethral-vaginal fistula that required closure. Ten patients required a secondary operation for persistent wetting. One patient had an artificial sphincter placed (Rosen type). It worked well but later eroded the urethra and was removed. Many successes have been reported with the use of artificial sphincters;[26,27] however I prefer to avoid them, opting to surgically narrow the outlet and use catheterization to empty if necessary.

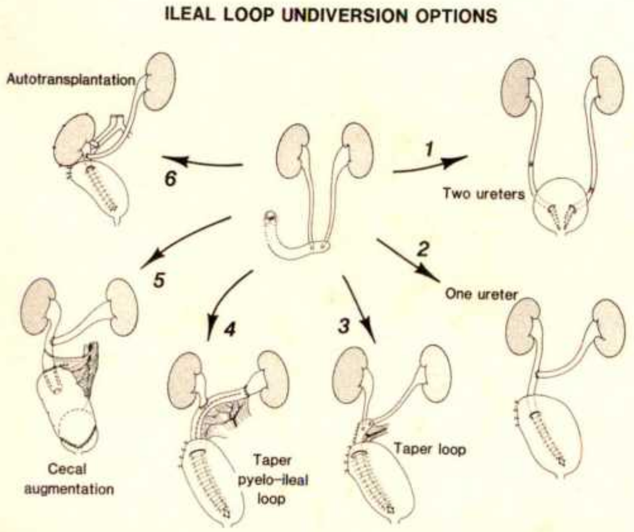


FIG. 4. Some options in undiverting patients with an ileal loop.

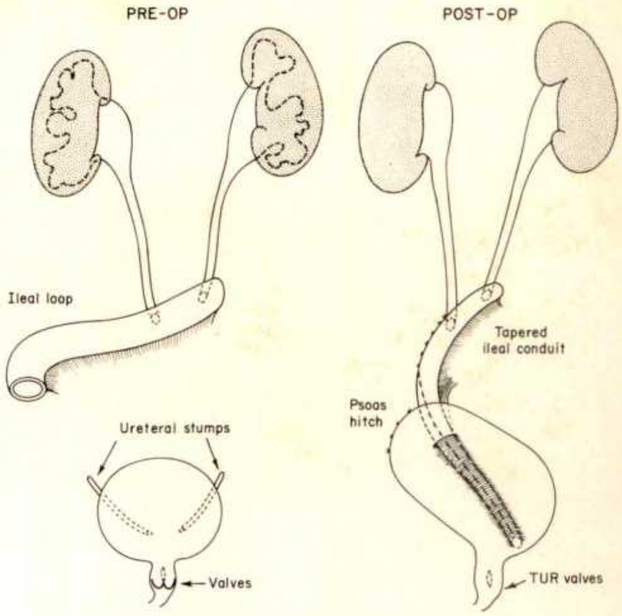


FIG. 5. Case 1, pre- and postoperative anatomy.

The following cases will present, in part, the spectrum of urinary undiversion. Ileal loop was the most common type of urinary diversion that was reversed. Figure 4 shows some of the options that may be used to reconstruct such a case. It is important to emphasize that the final decision as to how an individual case is best reconstructed should be deferred until operation when all of the anatomy is exposed and assessed, judging the length of ureters, the size and compliance of the bladder, and so on.

Case 1 (Figs. 5 and 6)

An 11-year-old boy was referred in January 1974 with an ileal loop for undiversion. He first had urinary infection at age 3 months; cystography showed hydronephrosis and massive reflux. He had suprapubic tube drainage of the bladder for 2 years. Stones were removed from both kidneys. At age 3 years the ileal conduit was performed. He improved, but at age 3.5 years underwent a second nephrolithotomy on the left side. Simultaneous cystogram and loopogram (Fig. 6A) showed a small bladder and satisfactory ileal conduit. The ureters were moderately dilated, as were the upper tracts. When his bladder was filled, he seemed to have normal sensation but could not void. At the time of operation cystoscopy showed previously untouched urethral valves. They were resected endoscopically. The ileal loop was tapered and reimplanted with a long submucosal tunnel. After operation there was frequent urination, but during the next month he experienced normal frequency and control, with a bladder capacity of 350 mL. This patient was one of those described in 1974.[1] During the next 16 years he lived a normal life. A recent intravenous pyelogram (IVP), 14 years after undiversion, is stable (Fig. 6b). The patient is now 27 years old. He is 6 feet 3.5 inches tall, healthy, asymptomatic, and normotensive. His creatinine clearance is 48 L/m^2 body surface area per day (L/m^2/BSA), *i.e.*, about 50% of normal.

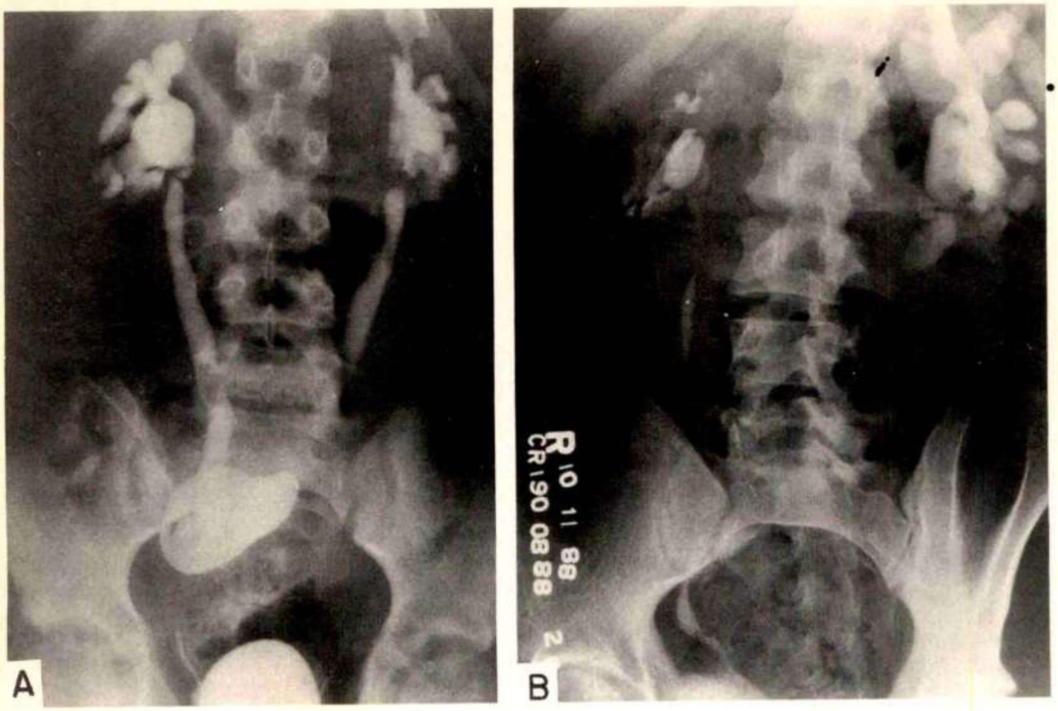


FIG. 6. Case 1, roentgenograms. (A) Preoperative retrograde filling of ileal loop and bladder. Note small size of bladder. Moderate upper-tract dilatation. (B) Postoperative IVP 14 years after undiversion. Stable upper tracts. Note right lower ureter, which is tapered bowel.

Comment

An ileal loop can be tapered and reimplanted like a ureter only if there is an ideal bladder in which a long submucosal tunnel can be constructed, using the adjunct of a psoas hitch. The tunnel length to 'ureter' diameter ratio must be about 5 to 1 if reflux is to be prevented. Thus this method of undiversion is not possible with a small, scarred bladder. I used this method in 28 cases. It was successful in 19; six needed lengthening of the tunnel to stop reflux. In three cases in which the bladder was too small, ileocecal augmentation was performed to stop reflux. Whenever bowel is used as a pseudoureter, the patient must be kept under continuing surveillance indefinitely. It is well known that late stricture is a complication of ileal loops. Similarly I have seen late stenosis occur in a bowel ureter;[28] three late stenoses occurred in these patients.

All of this patient's surgery resulted because his urethral valves were not diagnosed when he first presented with urinary infection at age 3 months. It is much less likely that this could occur today when valves are usually suspected in a male infant with hydronephrosis and reflux. Today a male infant with urethral valves would be treated with catheter drainage of the bladder for several days, while correcting dehydration, acidosis, and infection, followed by endoscopic resection of the valves.[29-32] Often nothing more is needed. If present persisting reflux or ureteral obstruction can be corrected later. Rarely is any type of diversion needed.

Case 2 (Figs. 7 and 8)

A 15-year-old girl was referred in 1982. There was sacral agenesis, but the patient had good sensation of the perineum and could contract the anorectal sphincter and levators. Bowel control was good. Y-V plasty had been done to the bladder neck at age 3 years. The ileal loop was performed at age 5 years because of increasing hydronephrosis and incontinence.

Cycling the bladder for 3 months through a percutaneously placed suprapubic tube did not increase the capacity of her small bladder. Undiversion consisted of narrowing the bladder neck and urethra to increase

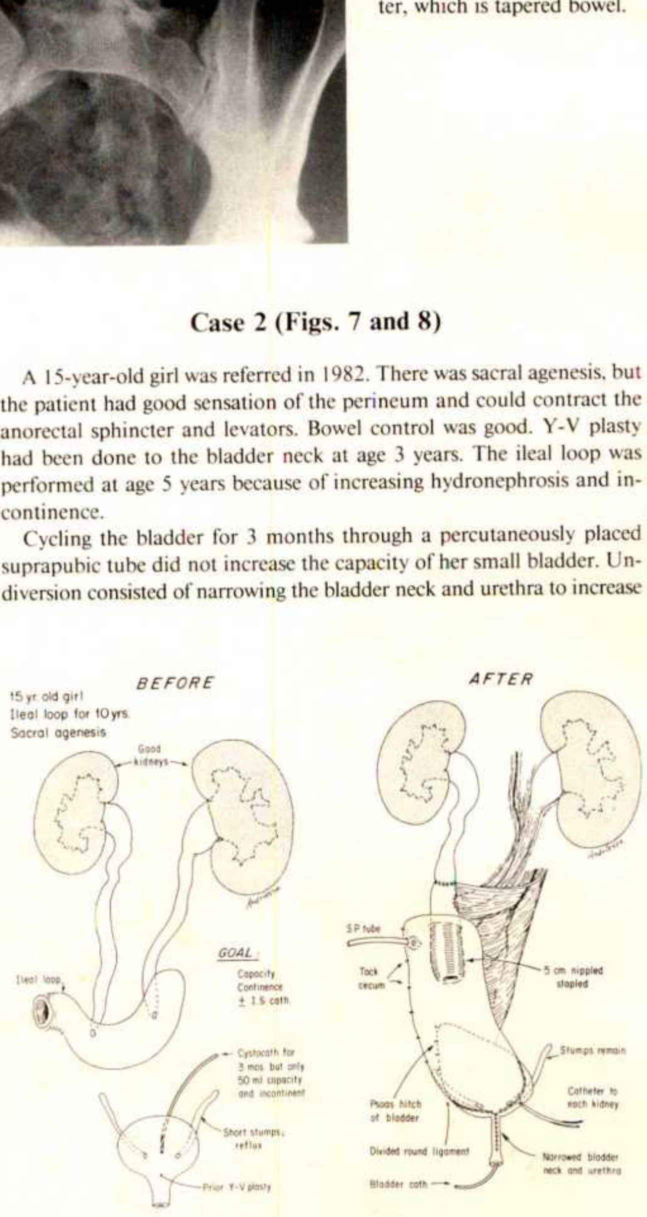
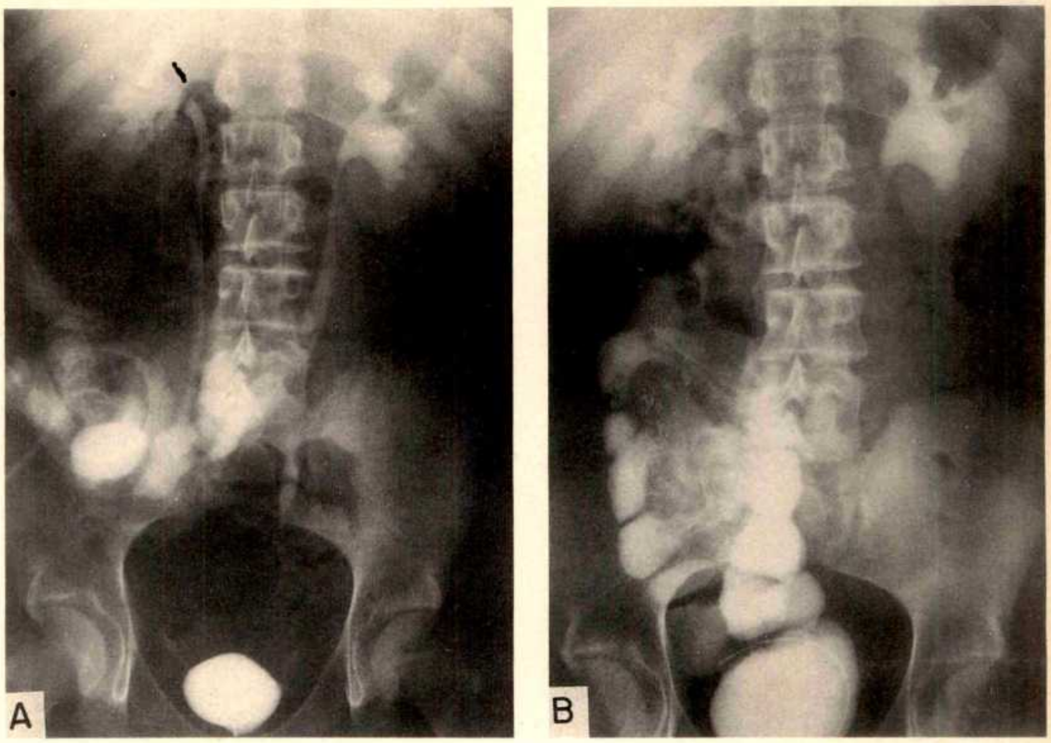


FIG. 7. Case 2, pre- and postoperative anatomy.



FIGS. 8A and B. Case 2, roentgenograms. (A) Preoperative retrograde filling of ileal loop and bladder. Note good upper tracts, sacral agenesis, and very small bladder. (B) Postoperative IVP. Stable upper tracts. Filling defect in cecal augmentation is antireflux nipple with staples visible. Catheter in bladder was clamped during IVP study. Patients with staples in urinary tract are routinely cystoscoped several months after operation to remove any staples that are not covered by mucosa because stones will form on these staples.

outlet resistance and augmenting the bladder with cecum. The ureters were not satisfactory for reimplantation into the bladder or into the cecal wall. An antireflux mechanism was constructed by intussuscepting the terminal ileum to make a nipple, stapling the nipple, and sewing it to the back wall of the cecum. The right ureter was joined end to end and the left ureter end to side into the terminal ileum. The patient catheterizes with a metal catheterizing sound. Postoperative urodynamic study showed urethral resistance of 85 cm of water, with a functional urethral length of 3.5 cm. The bladder capacity was 400 mL. The cecum did not exert uninhibited contraction waves. The patient has done well during the 8 years since undiversion. She empties the bladder without difficulty by self catheterization. She is dry, free from urinary infection, and her kidneys have remained stable by intravenous pyelography.

Comment

Cecal cystoplasty was performed as the means for augmentation in 38 patients. The intussuscepted nipple can prevent reflux, but it must be sewn to the back wall of the cecum or the nipple will pop out of the cecum and allow reflux.[33] In our initial efforts with cecal cystoplasty, I did not sew the nipple down. Some cases required reexploration to reintussuscept a nipple that popped out and sew it down.[13] When there is no terminal ileum to intussuscept, if an ileal loop has been taken very close to the cecum, I have fashioned a 'ureter' from tapered small bowel and implanted it in a submucosal tunnel in the back of the cecum. There has been a recent report in which ileocecal augmentation was performed in a patient with myelodysplasia, which resulted in diarrhea, which required putting the ileocecal valve back into the gastrointestinal tract.[34] Many patients with spina bifida and neurogenic bladders have alternating constipation and overflow diarrhea. Therefore it may be better to retain the ileocecal valve in that group of patients if another alternative can be used.

Case 3 (Figs. 9 and 10)

A 17-year-old girl was referred in 1987 for urinary tract reconstruction. During infancy she had closure of a meningocele and ventricular peritoneal shunt for hydrocephalus. At age 2 years an ileal loop was performed

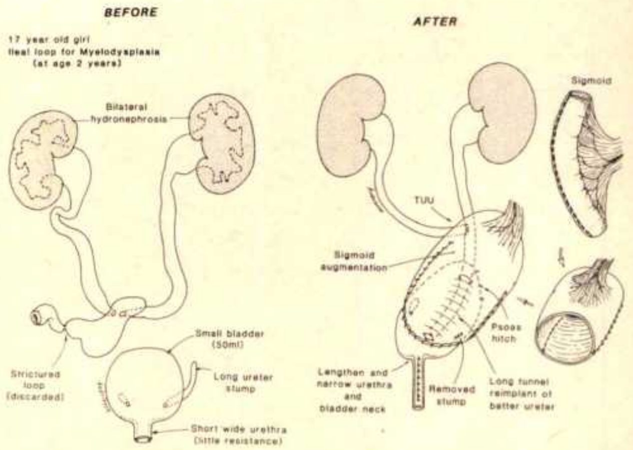
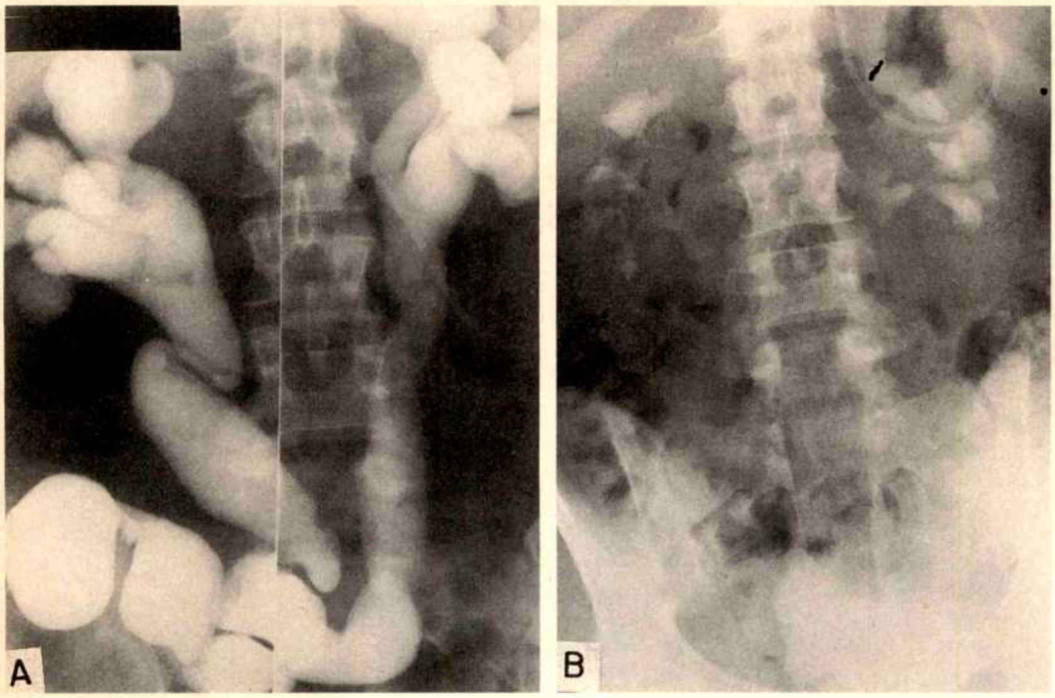


FIG. 9. Case 3, pre- and postoperative anatomy. Note reconfiguration of bowel augmentation, which dampens its peristalsis and increases its volume.



FIGS. 10A and B. Case 3, roentgenograms. (A) Preoperative retrograde loopogram showing multiple strictures of ileal loop, massive reflux, and hydronephrosis. The patient had long-term recurring urinary infections. (B) Postoperative IVP that shows relatively delicate upper tracts that are draining well into bladder augmented with sigmoid. Cystogram showed no reflux. Unexpectedly this patient does not require intermittent catheterization to empty the bladder.

for urinary incontinence of the myelodysplastic bladder. During the next 15 years there were many episodes of infection. There was progressive dilatation of the upper tract and multiple strictures of the ileal loop. Bladder cycling was not performed because the bladder was completely incontinent when filled with saline.

At operation the urethra was lengthened and narrowed to increase outlet resistance. It was possible to reimplant the left ureter, with a psoas hitch, draining the right ureter by transureteroureterostomy. A 30-cm-long segment of sigmoid colon was detubularized and reconfigured to augment the bladder. She tolerated this 16-hour operation well. Now 3 years later, the patient is well and free from urinary infection. She is maintained on prophylactic medication. Unexpectedly she is able to void by abdominal effort and crede maneuver, which she does every 3 or 4 hours to empty the bladder. She has been instructed, however, to catheterize at least twice daily, in the morning and evening, to ensure that the bladder is emptied completely. Urodynamic study after operation showed the bladder capacity to be 550 mL, with very little rise in pressure during filling. At capacity there were contraction waves from 10 to 30 cm of water, but they caused no leakage. Resistance at the repaired bladder neck measured 60 cm of water.

Comment

This patient was an ideal candidate for undiversion because she is an intelligent and highly motivated teenager who was anxious to be free of the bag on her abdomen and recurrent episodes of infection. She and one other female patient are the only patients of the 18 neurogenic bladder cases in this series who can void most of the urine without self catheterization. It is still important, however, to check at least twice daily to avert over distention and possible spontaneous perforation of the bowel segment in a patient with myelodysplasia and diminished sensation. Urinary diversion was a very common operation for this type of patient 10 to 20 years ago. There are, therefore, many like this patient who could be undiverted today. Her long-term outlook will be greatly improved not only because she is free from recurrent infection from reflux but also because her social status is greatly improved. Her upper urinary tract is much more delicate in appearance than it was originally.

Case 4 (Figs. 11 and 12)

A 19-year-old young man was referred in 1986 for urologic reconstruction. Urinary infection had occurred and study showed a very large bladder with massive reflux. At age 9 years ureteral reimplantation and 50% cystectomy were performed. He continued to have severe infection

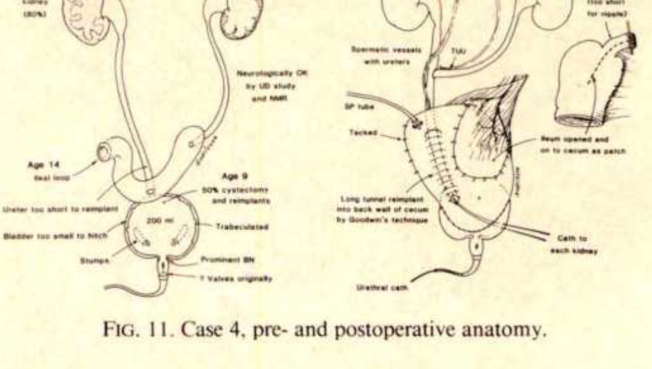
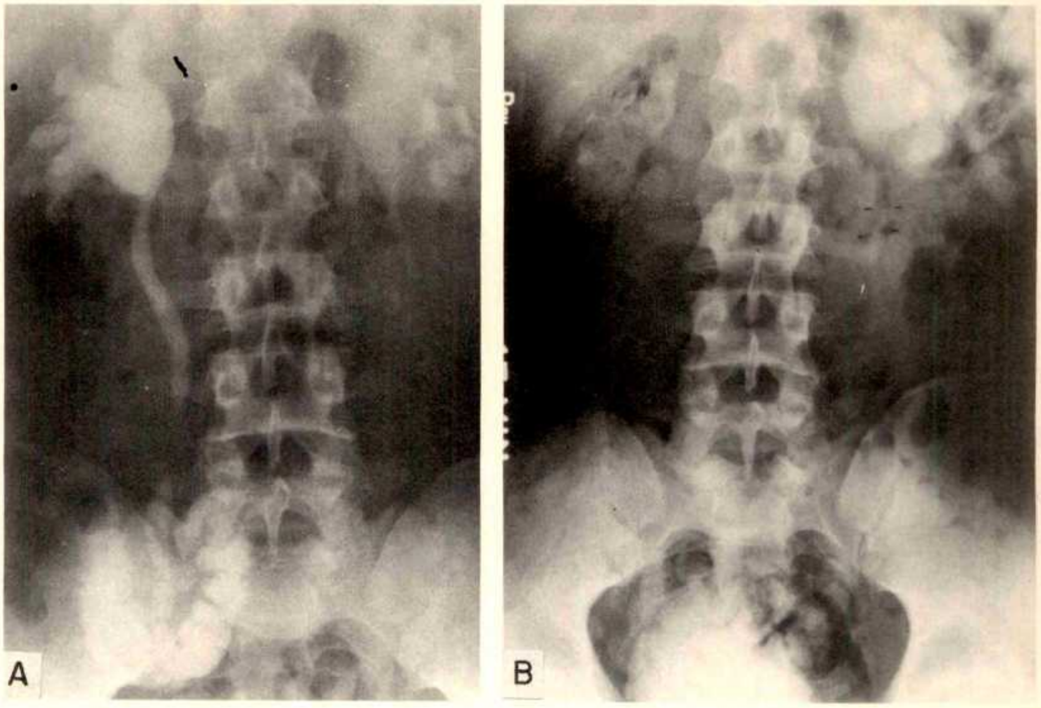

BEFORE
AFTER
Age 19 years
Better kidney (80%)
Scarred (20%)
Neurologically OK by UD study and NMR
Age 14 ileal loop
Age 9 50% cystectomy and reimplants
Ureter too short to reimplant
200 ml
Trabeculated
Bladder too small to hitch
Stumps
Prominent BN
? Valves originally
Only 2 inches of ileum (too short for nipple)
Spermatic vessels with ureters
TUU
SP tube
Tacked
Ileum opened and on to cecum as patch
Long tunnel reimplant into back wall of cecum by Goodwin's technique
Cath to each kidney
Urethral cath

FIG. 11. Case 4, pre- and postoperative anatomy.



FIGS. 12A and B. Case 4, roentgenograms. (A) Preoperative IVP. (B) Postoperative IVP. Upper tract stable.

with deteriorating upper tracts and thus ileal loop was performed at age 14 years. Magnetic resonance imaging of the lumbosacral spine was performed to rule out a spinal cord malformation because the etiology of his bladder problem was not clear. The study was normal. Bladder cycling was not attempted because much of the bladder had been surgically removed. The bladder was augmented with cecum. The right ureter was implanted using a submucosal tunnel in the back wall of the cecum. The terminal ileum was too short to make a nipple to prevent reflux, but that did not matter because the right ureter was very satisfactory to use for a tunnelling reimplantation, which is the preferred method in any event. The terminal ileum was opened and laid on to the anterior wall of the cecum to render it incapable of producing strong peristaltic waves. Transureteroureterostomy was performed. His preoperative urodynamic study showed normal urethral sphincter function. As expected he proved able to empty the bladder without difficulty after operation. He is clinically well. His blood urea nitrogen measures 20 mg/dL and his serum creatinine level is 1.3 mg/dL, (normal is 0.5 to 0.8 mg/dL). Creatinine clearance measures 54 L/m^2/BSA. His postoperative status has been well, except for one episode of epididymitis and traumatic small bowel perforation in an industrial accident.

Comment

Early detection of urinary infection and technically successful ureteral reimplantation would have almost certainly prevented the severe scarring with which he presented, in which very little function remained in the left kidney. Enlargement of the bladder is common with massive reflux. That enlargement would probably have disappeared with technically successful antireflux surgery. Thus partial cystectomy was probably not necessary at age 9 years, and it made necessary augmentation of the bladder as part of his reconstructive surgery.

Case 5 (Figs. 13 and 14)

A 15-year-old boy with prune belly syndrome was referred in 1975. Bilateral nephrostomies were performed at birth. An ileal loop was performed at age 1 year and revised at age 6 years, but it never drained. At age 14 years he was re-explored and it was found that the ileal loop had been placed backwards. It was removed and a new ileal conduit was performed. That too did not drain because both ureters were obstructed, the right at the ureteropelvic junction and the left by the crossing left colic artery. Undiversion included end-to-end anastomosis of the left renal pelvis to the proximal end of the ileal loop, moving the right renal pelvis more proximally, and tapering and implanting the loop with a psoas hitch. Nephrostomy drainage was eliminated 2 weeks after operation. Creatinine clearance was 30 L/m^2/BSA. The patient's clinical status was excellent during the next 9 years. At age 25 years, after treatment of a duodenal ulcer with Cimetidine, the serum creatinine rose to 12 mg/%. Dialysis was begun and he received a kidney transplant from his brother. Now age 31 years, and 6 years after transplantation, the patient is in good general health and works full-time as a stock broker.

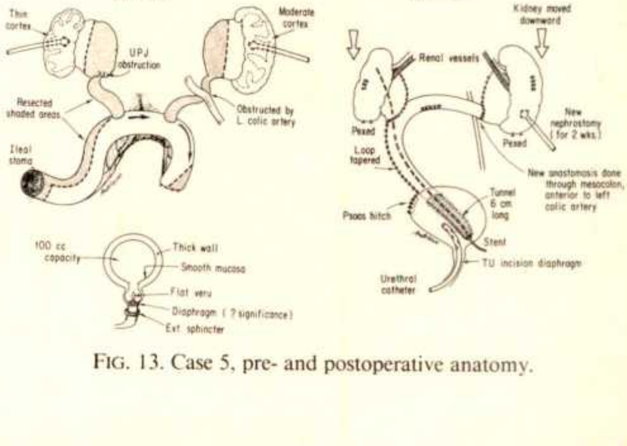
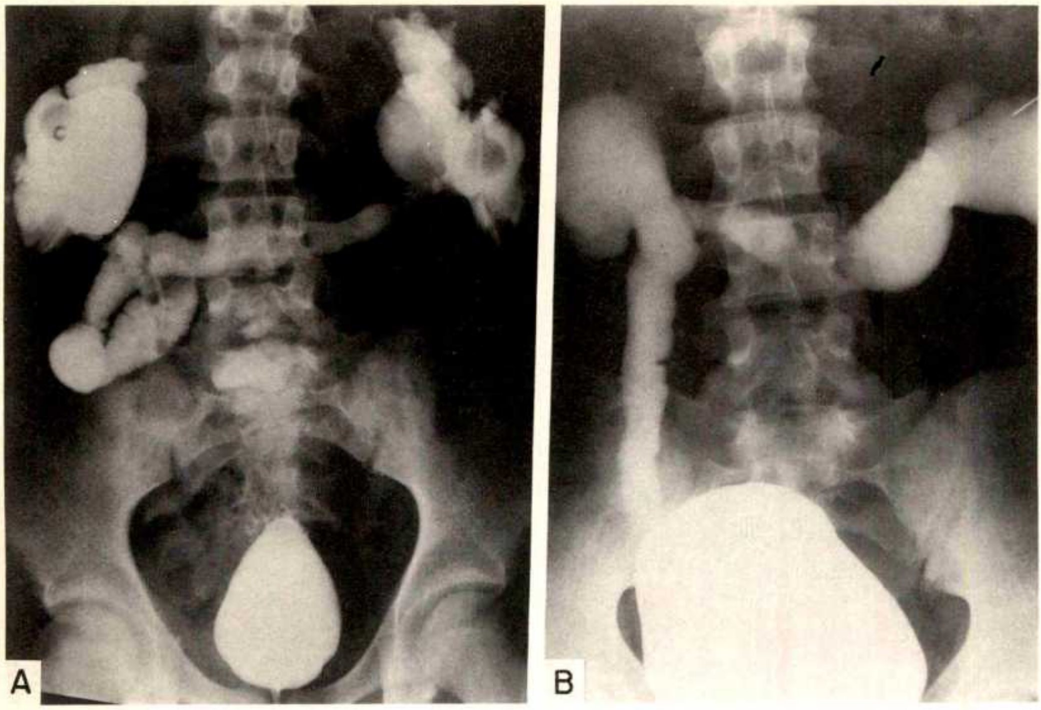


FIG. 13. Case 5, pre- and postoperative anatomy.



FIGS. 14A and B. Case 5, roentgenograms. (A) Preoperative filling of upper tract *via* 2 nephrostomy tubes and catheter in ileal loop stoma, and contrast in defunctioned bladder. (B) Postoperative antegrade study (note tip of needle in left kidney) showing tapered and implanted pyeloileal conduit. Note bladder now of normal size. Cystogram showed no reflux. The patient required renal transplantation 10 years after undiversion.

Comment

This patient is typical of the 14 patients with pyeloileal conduits treated by tapering the distal conduit to improve emptying and tunnelled implantation of the conduit into the bladder. Bladder cycling was not used in 1975, but his bladder, which had been defunctioned since birth, increased in size and functioned well nevertheless. Nephritis is a rare complication of Cimetedine. Evidently this tipped a precarious balance with his renal function, which had been stable for several years previously. Considering the very bad state of his kidneys at birth, he represents a striking example how careful metabolic management by a knowledgeable nephrologist prevented the need for renal transplantation for a remarkable length of time, 25 years.

Case 6 (Figs. 15 and 16)

A 12-year-old boy was referred in 1975 with a strictured ileal loop and a parastomal hernia. Previous surgery included nephrostomies and suprapubic cystostomy at age 1 month, resection of urethral valves at age 6 weeks, resection of the bladder neck at age 6 months, two operations for urinary incontinence, and an ileal loop at age 8.5 years. There was a good right ureteral stump without reflux. The right ureter of his horseshoe kidney was joined to it, and the left side of the horseshoe was drained by left-to-right ureteropyelostomy. By splitting the pubic symphysis for exposure, the urethra and bladder neck were narrowed extensively to provide more outlet resistance. The bladder increased gradually in size. There was urinary wetting initially, but it disappeared during the next 2 years. The patient is now age 26 years, has full-time employment, and is in good general health. However he has psychologic problems secondary to multiple hospitalizations as a young child.

Comment

Endoscopic resection of the urethral valves during infancy probably would have sufficed in this patient who had tube diversion, open resection of valves, which left him incontinent, followed by failed surgery for incontinence, and finally an ileal loop for permanent urinary diversion. Modern fiberoptic infant panendoscopes have changed greatly the treatment of urethral valves during infancy in recent years. I have found that splitting the symphysis pubis has proved key in achieving urinary con-

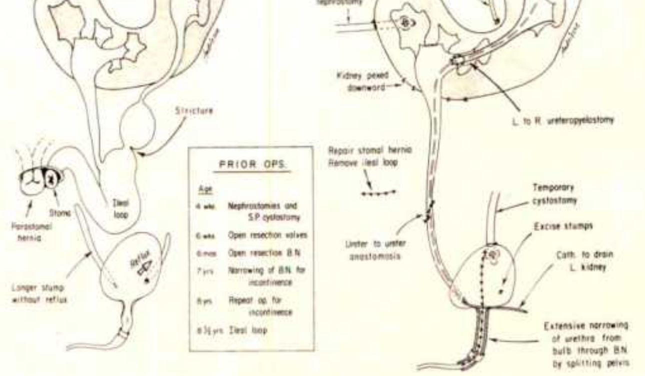
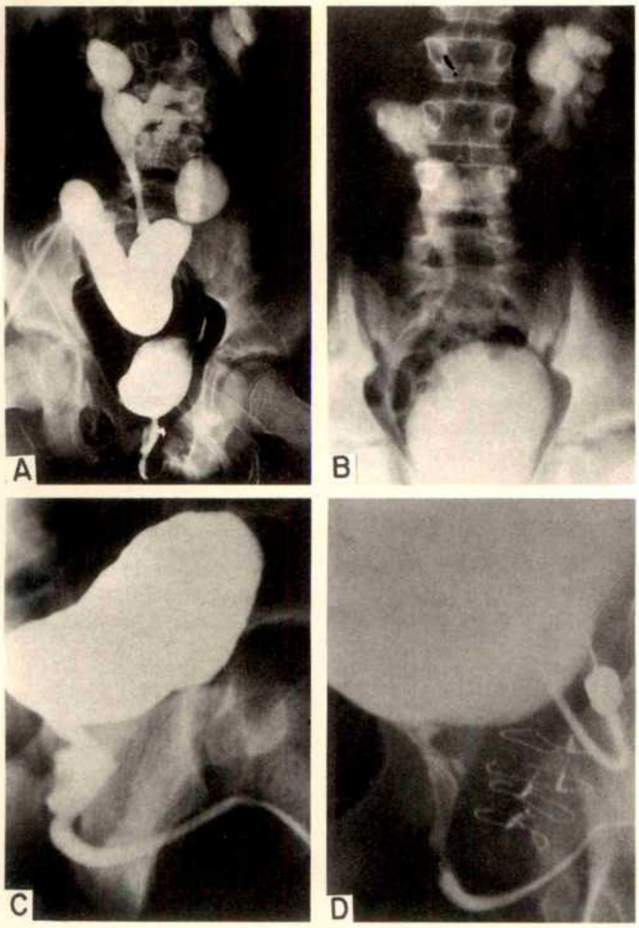

BEFORE Age 12 yrs.
Horseshoe kidney
Stricture
Stoma
Ileal loop
Parastomal hernia
Longer stump without reflux
Reflux
PRIOR OPS.
Age
4 wks Nephrostomies and S.P. cystostomy
6 wks Open resection valves
6 mos Open resection B.N.
7 yrs Narrowing of B.N. for incontinence
8 yrs Repeat op. for incontinence
8½ yrs Ileal loop
AFTER
Divided L. colic artery which crossed L. ureter
Temporary nephrostomy
Kidney pexed downward
L. to R. ureteropyelostomy
Repair stomal hernia Remove ileal loop
Temporary cystostomy
Excise stumps
Ureter to ureter anastomosis
Cath. to drain L. kidney
Extensive narrowing of urethra from bulb through B.N. by splitting pelvis

FIG. 15. Case 6, pre- and postoperative anatomy. Splitting the symphysis pubis was used to narrow the urethra and bladder neck.



FIGS. 16A–D. Case 6, roentgenograms. (A) Preoperative loopogram and cystogram. (B) Postoperative IVP. It has remained stable for 15 years. (C) Preoperative cystogram of defunctioned bladder. Note wide prostatic urethra, despite two previous attempts to narrow bladder outlet. (D) Postoperative cystogram (note needle in bladder) showing narrowed prostatic urethra and higher bladder neck. The patient is now continent. Splitting the symphysis pubis was key in this repair.

tinence in patients like this who require narrowing of the urethra and bladder neck to increase outlet resistance.[35] A high-pressure small-volume noncompliant 'valve bladder' is developed in some boys with urethral valves.[36,37] Augmentation is needed in some to prevent back pressure on their upper tracts.

Case 7 (Figs. 17 to 20)

This 9-year-old boy was referred in 1976 with a strictured ileal loop and hydronephrosis and a small scarred bladder following chemotherapy and radiation therapy for sarcoma of the prostate 4 years before. A nonrefluxing colon conduit was constructed to save his kidneys from increasing hydronephrosis and infection (Fig. 17). The bladder was extremely fibrotic and it was decided to defer undiversion. Five years later total obstruction of his membranous urethra and secondary pyocystis developed. The stricture was repaired (Fig. 18); the bladder was still small, but the bladder neck was no longer densely fibrotic as it had been 5 years earlier. After the stricture repair, the patient could hold saline instilled into the bladder. Undiversion was performed (Fig. 19) by adding the cecum to the bladder and joining the nonrefluxing colon conduit to it. The patient is now 23 years old. He voids well by abdominal effort. He is dry, sexually active, and has excellent renal function and stable upper tracts.

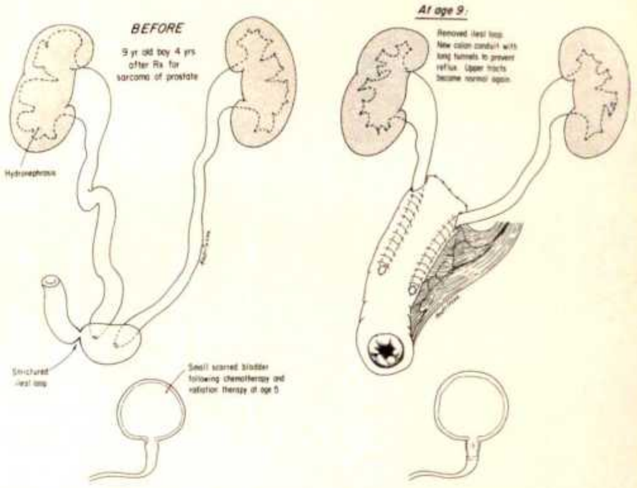

BEFORE
9 yr old boy 4 yrs after Rx for sarcoma of prostate
Hydronephrosis
Strictured ileal loop
Small scarred bladder following chemotherapy and radiation therapy at age 5
At age 9:
Removed ileal loop. New colon conduit with long tunnels to prevent reflux. Upper tracts became normal again.

FIG. 17. Case 7, preoperative anatomy and following nonrefluxing colon conduit. Upper tracts then improved dramatically by roentgen follow-up.

Comment

This patient is 1 of 13 patients who had a nonrefluxing colon conduit made with the plan to later consider undiversion if it should prove feasible. He demonstrates well how radiation therapy and chemotherapy can cure some

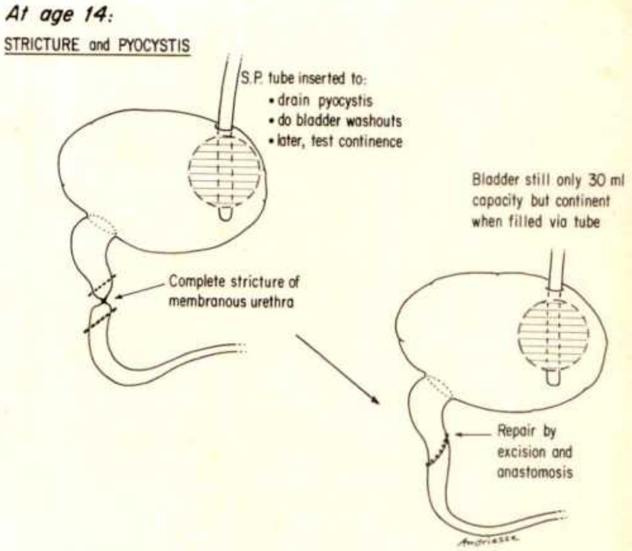

At age 14:
STRICTURE and PYOCYSTIS
S.P. tube inserted to:
• drain pyocystis
• do bladder washouts
• later, test continence
Bladder still only 30 ml capacity but continent when filled via tube
Complete stricture of membranous urethra
Repair by excision and anastomosis

FIG. 18. Case 7, urethral stricture and its repair at age 14 years when pyocystis developed.

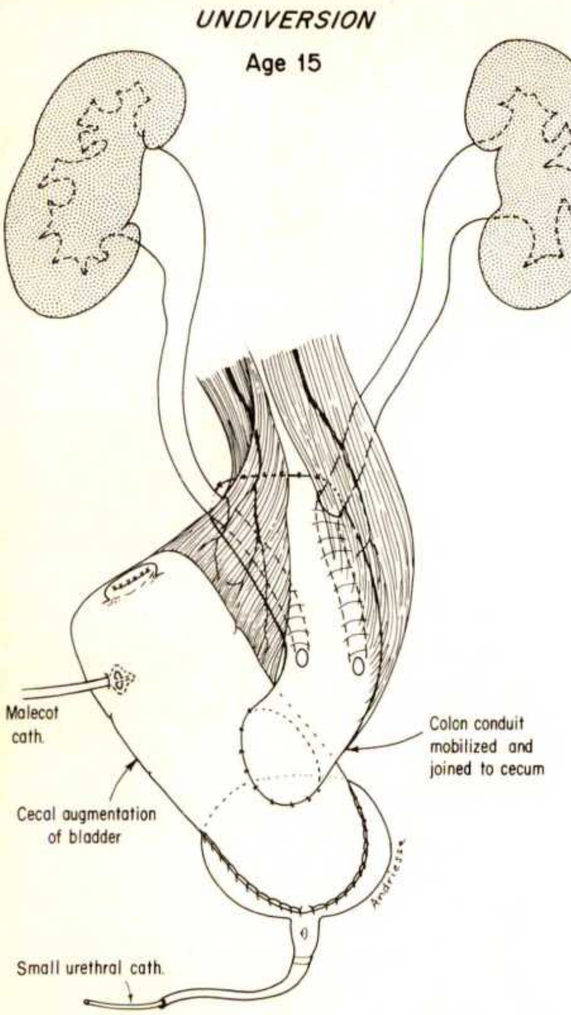

UNDIVERSION
Age 15
Malecot cath.
Colon conduit mobilized and joined to cecum
Cecal augmentation of bladder
Small urethral cath.
Andriesse

FIG. 19. Case 7, anatomy using composit augmentations.

genitourinary rhabdomyosarcomas but then leave a badly scarred urinary tract that requires major reconstructive surgery. He is continent despite stricture resection at the site of the membranous urethra because the bladder neck is intact. Voiding is accomplished by abdominal effort, which raises intravesical pressure, while simultaneously voluntarily opening the bladder neck.

Case 8 (Figs. 21 and 22)

A 14-year-old boy was referred in 1982 with an ileal loop that was performed after unsuccessful ureteral reimplantation surgery. The bladder size increased rapidly during 1 week of hydrostatic stretching. Continence and voiding were satisfactory when it was filled with saline. Because his ileal loop was strictured, it could not be used as a small bowel ureter. It was thought that this could happen again if a new segment of bowel was used to fashion a ureter. Therefore the right kidney was autotransplanted to the right lower quadrant, giving ample length for a tunnelled reimplantation of the ureter. Left-to-right transureteropyelostomy was performed. The patient, now age 24 years, works full-time as a mechanic, has a child, and is free from urologic problems.

Comment

Autotransplantation of the kidney was performed in two cases. Each of these patients had two good kidneys, which gave a margin for error that would not be present with patients who have poor function. Because there was a good ureter and a good bladder for ureteral reimplantation, but length was deficient, autotransplantation seemed reasonable.

Case 9 (Figs. 23 to 25)

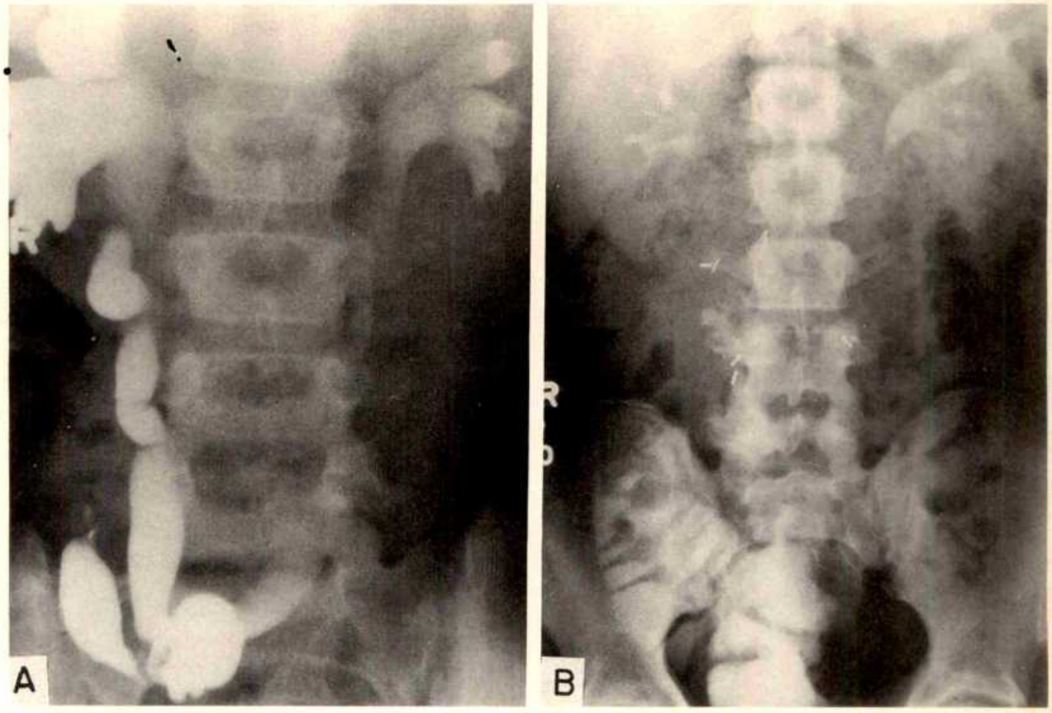
A 3-year-old girl was referred in 1988 for reconstructive surgery. Born with severe bilateral obstructive megaureters and hydronephrosis, bilateral end ureterostomies were performed at age 1 month. The ureterostomies did not drain well. Therefore bilateral loop cutaneous ureterostomies were performed at age 1 year. Hydronephrosis improved. The ureterostomies were later closed, but severe hydronephrosis recurred.

Preoperative assessment showed the bladder volume to be only 10 mL. When contrast was introduced through the end ureterostomy stomas, the ureters drained well but contrast remained in the kidneys, indicating functional ureteropelvic junction obstruction on both sides. At operation the better ureter was reimplanted with as long a tunnel as possible in her tiny bladder, together with psoas hitch. Transureteroureterostomy drained the opposite ureter. Both upper ureters were obstructed from angulation at the site of the ureterostomy closures. Therefore bilateral dismembered pyeloplasties were performed, maintaining ureteral blood supply in the surrounding periureteral tissues. The bladder was augmented with a large patch of stomach wall, based on the right gastroepiploic artery. The patient tolerated this 13-hour operation well. Bladder emptying was performed initially by intermittent catheterization by her mother. Gradually she learned to void to completion and catheterization was stopped. Postoperative evaluation showed reflux. Subureteric injection of teflon paste beneath the ureteral orifice stopped the reflux.[38] Now 2 years after operation, the patient voids normally, is dry, and free from urinary infection. Blood chemical values are remarkably normal considering the degree of hydronephrosis originally present: BUN 10 mg/%, serum creatinine 0.3 m/%, and creatinine clearance 121 4/m^2/BSA. Postoperative urodynamic study showed bladder capacity to be 275 mL, with no uninhibited contractions, and normal sphincter function.

Comment

Use of the stomach for bladder augmentation has some outstanding advantages over small bowel and colon.[39–42] (1) It is metabolically superior regarding chloride absorption and base loss, seen with segments of small bowel and especially colon. Those segments tend to lose bicarbonate and potassium, and, to a lesser extent, sodium while resorbing chloride.[43,44] If potassium loss is replaced as potassium chloride, bicarbonate loss can be accelerated, aggravating acidosis. On the other hand, gastric mucosa secretes chloride ion and is, therefore, preferred in patients with poor renal function who can not tolerate increased solute resorption and the resulting acidosis. (2) The urine is more often sterile after operation because it is not so alkaline in pH. (3) Ureters can be tunnelled and implanted easily into gastric wall. (4) It is very durable yet compliant.

The stomach may be the only reasonable means for



FIGS. 20A and B. Case 7, roentgenograms. (A) Preoperative loopogram. Note severe ileal loop stricture, and dilated upper tracts. The patient was having recurrent urinary infection. (B) Postoperative IVP showing excellent upper tracts, which have remained stable.

reconstructing certain patients with cloacal exstrophy, who have little or no colon, and who have a short small bowel. Its metabolic superiority probably makes it the augmentation of choice in patients with very poor renal function. Two of fourteen patients for whom I have used gastrocystoplasty had pain in the region of the bladder, which was relieved by Cimetidine. Only 3 of the 14 were undiversion cases because I began using stomach wall for bladder augmentation only recently. These patients do not have excess mucous in urine, which is an added advantage, because mucous provides a nidus for stones. Because gastrocystoplasty has been used only recently in children, as compared to use of intestine and colon, long-term observations are needed. Cutaneous ureterostomy was a common type of temporary diversion in infants a few years ago.[45] It can cause many complications, however,[46] as shown in this case.

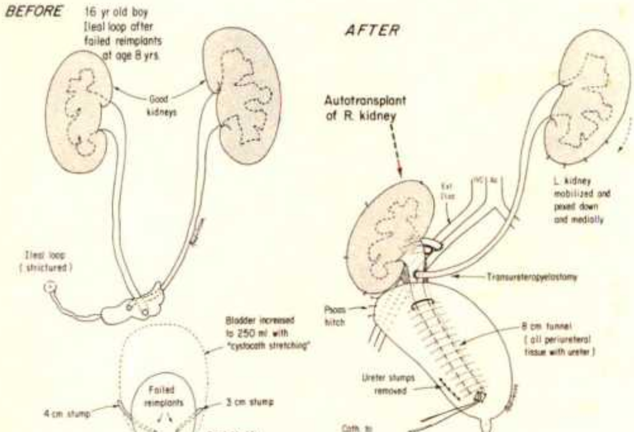


FIG. 21. Case 8, pre- and postoperative anatomy.

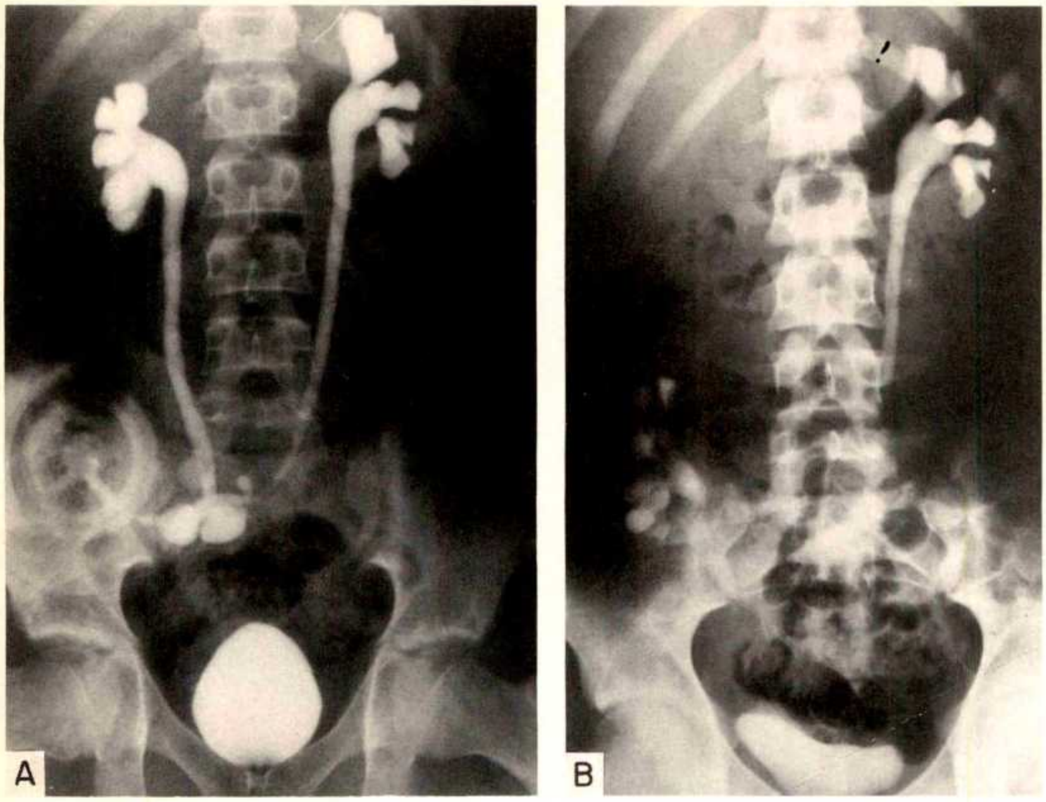
Case 10 (Figs. 26 to 28)

A 5-year-old girl was referred in 1980. At birth she was noted to have a severe cloacal malformation, with high confluence of the bladder, two vaginas, and the colon. More than half her life had been spent in hospitals. Previous operations included ureteral reimplantation, an attempt to exteriorize the vagina with a perineal flap, and rectal pullthrough for imperforate anus. Severe complications occurred, with marked contracture of the bladder and obstruction of the ureters. The right side had been drained by nephrostomy and the left by loop ureterostomy.

It was first necessary to create a urethra by a method previously described using vaginal mucosa and a buttocks flap.[13] Bladder cycling was begun, but the bladder did not stretch. Six months later undiversion was performed, reimplanting the better ureter, closing the loop ureterostomy, draining the right kidney by transureteroureterostomy, and augmenting the bladder. The patient is now age 15 years. She is dry, but must use intermittent self catheterization to empty the bladder. Her upper tracts and renal function are stable. She is free from fecal soiling, but must rely on a soap suds enema every 2 days to evacuate her colon.

Comment

I have described previously observations in reconstructing female infants and girls with cloacal malformations.[47,48] The urinary tract is the most life-threatening aspect of the malformation. In 39 secondary cases such as this, 19 had previous urinary diversions (ileal loop [4],



FIGS. 22A and B. Case 8, roentgenograms. (A) Preoperative loopogram and cystogram. Note long stricture of loop. (B) Postoperative IVP. Note kidney transplanted to right lower quadrant.

loop ureterostomy [5], and vesicostomy [10]). In nearly all of the secondary cases a definitive rectal operation had been done, but the more life-threatening urinary tract had not been repaired. After performing a divided right transverse colostomy in the neonate with a cloaca, I believe the infant should be evaluated radiographically and endoscopically before any other surgery is performed. In some a preliminary urologic procedure should be performed because more than half have vesicoureteral reflux. I am convinced that a preliminary rectal pullthrough should never be performed. The preferred approach for separating the bowel, vagina, and urogenital sinus is through a posterior sagittal approach.[49] The urogenital sinus should be maintained as a urethra. The vagina (often two of them) should be separated from the urogenital sinus and brought through to the perineum. If it will not reach the perineum, an extension of bowel can be joined to it. When the rectum is pulled through, it must be placed accurately within the pelvic muscle complex to provide the best chance for bowel continence. The advent of magnetic resonance imaging has revealed that many of these children have tethering of the spinal cord. Therefore their evaluation should include MRI examination. Neurosurgical detethering of the spinal cord can increase the chance for bowel continence. Although this patient has a reasonably satisfactory resolution of her many problems, most of them could have been avoided by techniques in current use for dealing with these complex malformations.

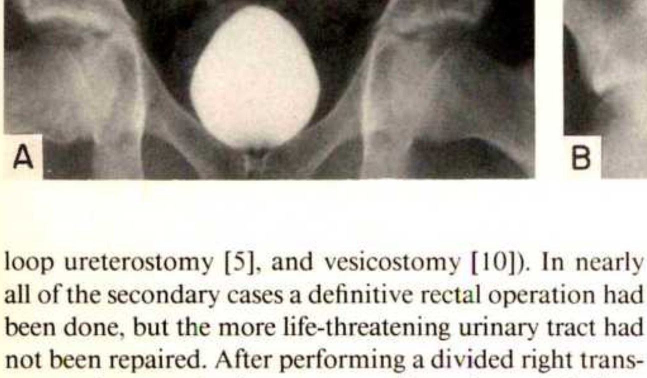
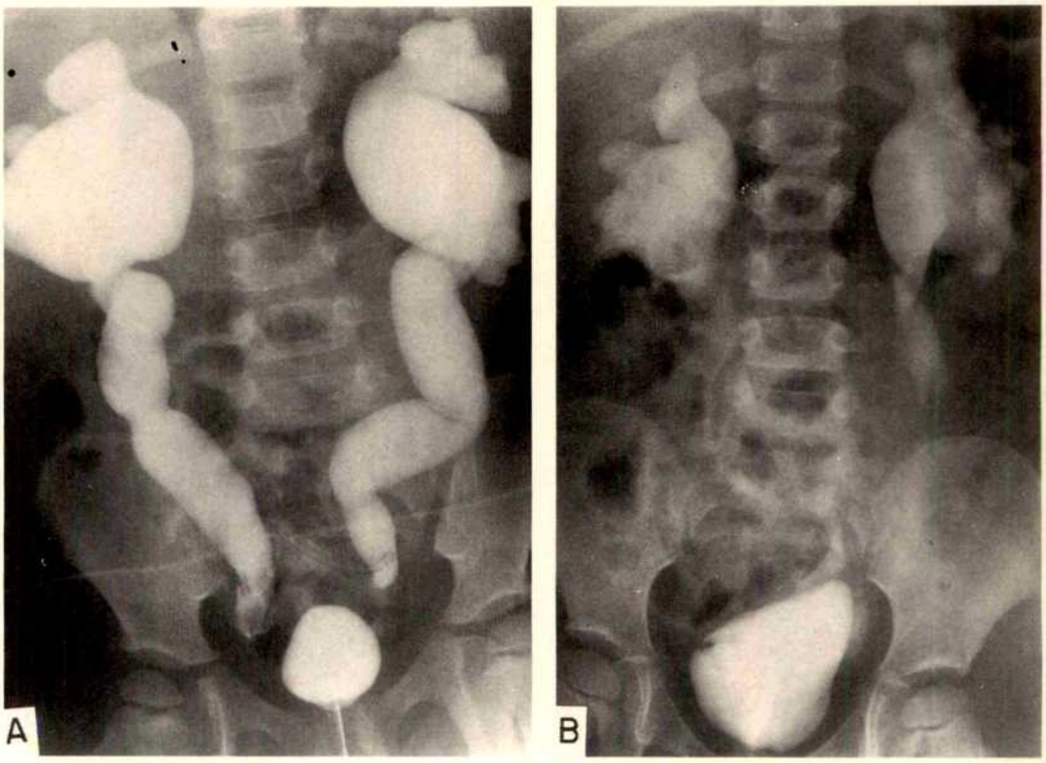

BEFORE
3 year old girl
End ureterostomies age 1 month (for obstruction)
Loop ureterostomies age 1 year. Right closed age 2. Left closed age 2 1/2.
Hydronephrosis
Prior bilateral nephrostomies
Kidneys rotated
Partial obstruction of both ureterostomy closures (from angulation)
End ureterostomies (but kidneys not draining well)
Tiny bladder 10 ml capacity
Normal urethra and bladder neck
AFTER UNDIVERSION
Stomach to augment bladder
Gastroepiploic artery
Kidneys rotated back into normal position
Pyeloplasties
Bladder augmentation with stomach
T.U.U.
Long tunnel reimplant
Psoas hitch
Cath

FIG. 23. Case 9, pre- and postoperative anatomy.

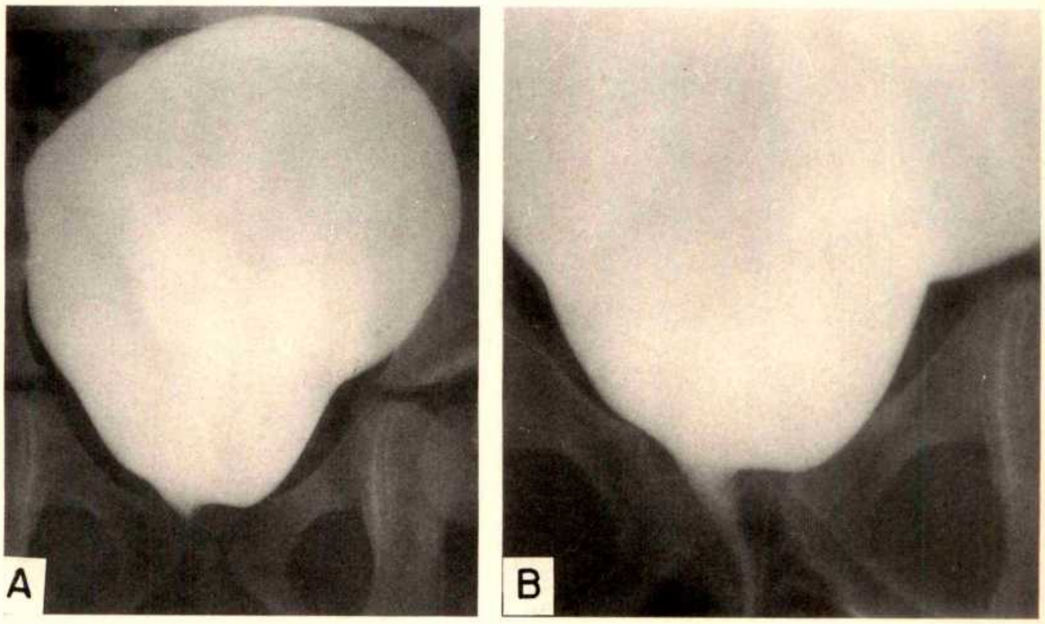
Discussion

Urinary diversion in infants and children has become needed much less often in the past decade in which there has been greater success in dealing with malformations for which surgical results were previously disappointing. Examples include urethral valves, neurogenic bladder, the exstrophy-epispadias complex, cloacal malformations, and so on. Although ileal loop urinary diversion was used



FIGS. 24A and B. Case 9, roentgenograms. (A) Preoperative simultaneous retrograde ureterograms and cystogram. Ureters emptied quickly, but contrast remained in renal pelvis on both sides, each being partially obstructed from angulation at closure of former ureterostomies. Note very small bladder. (B) IVP 1 year later. Upper tracts draining well, with less hydronephrosis.

widely in the 1950s and 1960s, retrospective review showed that the reflux present with ileal loops often caused damage to the upper tracts, especially if there stomal stenosis or stricture of the conduit.[50–53] Therefore the trend changed to performing conduits that did not allow reflux, such as the colon conduit with tunnelled ureteral anastomoses, or an ileal cecal conduit with reinforcement of the ileal cecal valve.[54–57] In the past decade great strides have been made in the use of continent diversions of various types in which two valve mechanisms are incorporated, one to prevent reflux to the upper tracts and another to prevent leakage at the stoma on the abdominal wall.[58–62] The urine is collected in an internal bowel reservoir and is emptied by intermittent catheterization. This obviates wearing an external bag. However I believe that every effort should be made to repair the bladder itself, even



FIGS. 25A and B. Case 9, roentgenograms. (A) Bladder filled to 275 mL. Most of the bladder wall is gastric augmentation. (B) Voiding film, showing normal bladder neck and urethra. Patient empties completely by abdominal effort while voluntarily opening the bladder neck and sphincter.

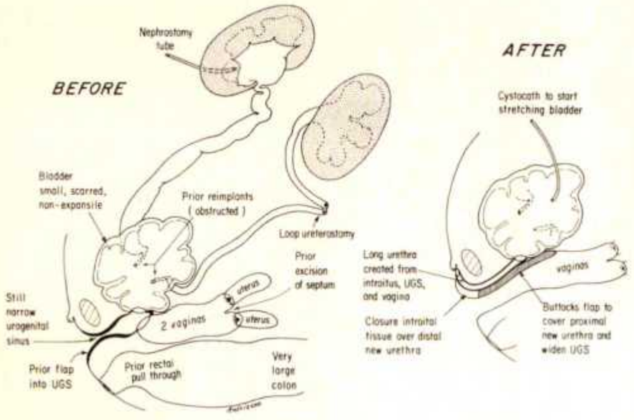

BEFORE
Nephrostomy tube
Bladder small, scarred, non-expansile
Prior reimplants (obstructed)
Loop ureterostomy
Prior excision of septum
uterus
uterus
2 vaginas
Still narrow urogenital sinus
Prior flap into UGS
Prior rectal pull through
Very large colon
AFTER
Cystocath to start stretching bladder
Long urethra created from introitus, UGS, and vagina
vaginas
Closure introital tissue over distal new urethra
Buttocks flap to cover proximal new urethra and widen UGS

FIG. 26. Case 10, preoperative anatomy and first stage of creating urethra. Urogenital sinus had been opened from below in an effort to exteriorize vaginas. However in cloacas the vagina should be disconnected and brought to the perineum, retaining the urogenital sinus as the urethra.

when more than one operation is needed. Only seldom do I perform continent diversions in children.

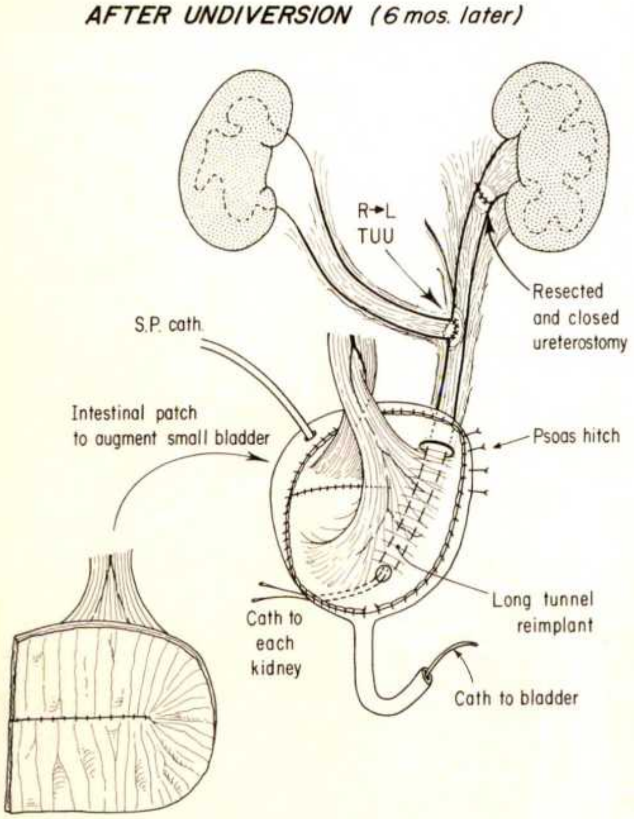
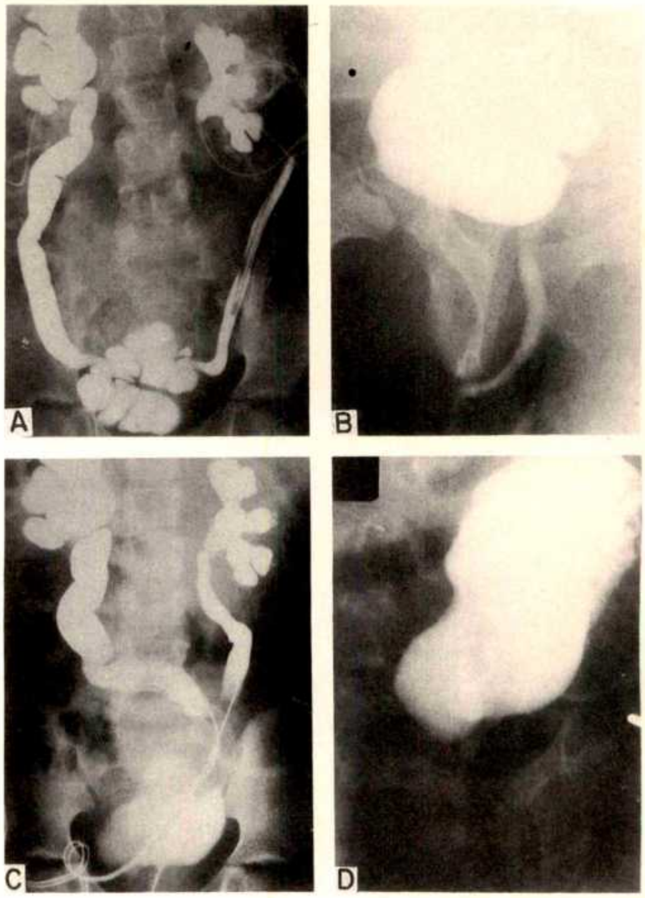

AFTER UNDIVERSION (6 mos. later)
R→L TUU
Resected and closed ureterostomy
S.P. cath.
Intestinal patch to augment small bladder
Psoas hitch
Long tunnel reimplant
Cath to each kidney
Cath to bladder
Ileum

FIG. 27. Case 10, anatomy after undiversion. Note simultaneous operation on both ends of left ureter as well as transureteroureterostomy in its mid portion. This can be accomplished if all periureteral tissue, as well as gonadal vessels, are retained with the lower ureter during its mobilization. I have not encountered atrophy of a gonad in a female or male by dividing the gonadal vessels in the lower abdomen and retaining them with the ureter as collateral.



FIGS. 28A–D. Case 10, roentgenograms. (A) Preoperative filling of urinary tract through right nephrostomy tube and left loop ureterostomy. Note extremely scarred and contracted bladder from previous surgery. (B) Cystogram after creation of new urethra from urogenital sinus and a buttocks flap. Bladder size unchanged, despite cycling. (C) Filling of urinary tract 10 days after operation *via* temporary stent catheters placed during undiversion. Note transureteroureterostomy. Later IVP showed great improvement in upper tracts, which have remained stable for the past 10 years. (D) Postoperative cystogram to show augmented bladder with normal capacity. Patient is dry, but empties by intermittent catheterization.

There are many patients who have been managed by various types of urinary diversions in the past who can be 'undiverted,' refunctionalizing the bladder. Many surgeons have contributed to the armamentarium that makes this possible. Some have been mentioned in a recent book on this subject.[12] Bricker's contribution of the ileal loop was a milestone in the incorporation of bowel into the urinary tract as a conduit.[63] It laid the foundation for using the small bowel as a substitute ureter and for increasing the capacity of the bladder.[64,65] The introduction of clean intermittent catheterization of certain patients by Lapides[15] made possible undiversion of patients who cannot void after being undiverted. It also allowed the concept of continent diversion, which is sometimes used in children.

Urinary undiversion should be considered for patients who have undergone diversion in the past. Reconstructions of this magnitude require meticulous attention to all technical surgical details. Many of these patients have poor renal function. However this is not a contraindication to undiversion because restoration of bladder function gives a much better quality of life. Furthermore it is better ultimately to transplant a kidney into a bladder than into a cutaneous diversion.[66] Undiversion may reduce urinary infection and prolong the time before transplantation is needed.

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DISCUSSION

DR. JAMES F. GLENN (Lexington, Kentucky): It is an honor and privilege to discuss this paper by Dr. Hendren, whom I am sure all of you recognize to be one of the pioneers in the field of undiversion. This enormous personal experience of 177 cases is remarkable for its magnitude, if for nothing else, but the results are formidable and admirable indeed.

Dr. Hendren, some 10 years ago, prepared a chapter for the textbook *Urologic Surgery*, on the subject of undiversion, and at that time it was indeed a pioneering adventure.

He has followed through with results that are certainly remarkable.

This elegant paper prompts several observations that I think should be emphasized. First, this is not one surgical technique, but a combination of many surgical advances.

Second a minor observation. The use of vaginal wall for reconstruction of the urethra is not only surgically tenable but embryologically warranted. Both the vagina and urethra have a common embryologic anlage, and indeed, a vaginal urethra will be functional in many instances, functional as far as urinary continence and control are concerned.

I think another point that should be emphasized is the importance of intermittent catheterization. In many instances undiversion or reconstruction or substitution of any portion of the urinary tract will result in continence but may not result in adequte voiding, particularly in instances of neuropathic disorder.

The introduction of clean intermittent catheterization by the patient four or five times daily has been a major advance in urologic management of patients.

I would point out also the deaths in this series were not related in any instance to the surgery itself but rather to other events that followed at a late stage, and that indeed is quite an accomplishment.

The use of stomach for bladder substitution is also unique. I believe that the first person to do that was Professor Ong of Hong Kong, who used the stomach. Many of us thought it was ludicrous at the time. We didn't believe that the stomach could be brought down into the pelvis satisfactorily. Later with personal experience, we found that this could, indeed, be done and the stomach proves to be a very fine bladder substitute.

I would point out also that in this series the form of diversion used most often was ileal conduit. Had this been done 20 years earlier, the most common form of urinary diversion would have been ureterosigmoidoscopy, and 20 years from now in the future I doubt that anyone will have this much experience in urinary undiversion, simply because we are moving toward newer techniques of substitution for ureter, for bladder, for urethra as a primary event in the management of urologic disorders. In other words, we are accomplishing urinary tract substitutions that are functional at the time of initial surgery rather than diverting the urinary stream.

On that basis we can regard Dr. Hendren's fine paper as an evolutionary step in the management of potential urinary diversion.

DR. KEITH ASHCRAFT (Kansas City): Dr. Hendren's experience with undiversion is truly remarkable. Those of us who deal with these difficult-to-manage patients have learned from Hardy that with a little bit of this and a little bit of that and some imagination, you can put together a unique operation tailored to the individual patient. You can change a miserable, wet, smelly child with deteriorating upper tracts into a patient whose quality of life is much improved.

Dr. Hendren has taught us as well that the common denominator to success is tenacity. If it doesn't work the first time, you operate again and again to achieve continence and freedom from appliances.

Successful undiversion will also often improve the length of life. Although some of these patients may go into end-stage renal disease, that process may be delayed by a period of years.

I have three questions for Dr. Hendren. Would you use the ileocecal segment only as a last resort for augmentation with the idea that an intact ileocecal valve is most desirable in the GI tract?

Second, also in the manuscript, you used artificial sphincter in only one patient and later removed it because of erosion. The difficulty that many of us have with this particular field in undiversion is creating a socially continent patient. What is the future of artificial sphincters?

And last the bowel exposed to the presence of urine in the old uretosigmoidostomy often underwent malignant change. Is there any incidence of malignancy that develops in the bladder that has been augmented with colon or other portions of the intestine?

DR. W. HARDY HENDREN (Closing discussion): I will begin by addressing the three questions by Dr. Ashcraft. First I do not use the ileocecal valve if there is a better alternative, particularly in myelodysplastic patients. Their stool continence is a balance between having constipation and overflow diarrhea. Therefore it may be better not to use their ileocecal valve in doing a reconstruction because this can result in loose stools in some patients. There have been some recent case reports that suggested that loss of the ileocecal valve caused diarrhea in a few former myelomeningocele patients.

Regarding the artificial sphincter, there are surgeons who implant this for urinary incontinence control. However the least good results have been in these types of patients who have had a lot of previous surgery and a scarred bladder outlet. Because we are working on young patients and are striving for 70- to 80-year survival without a lot of additional surgery, I have tried to work with the patients' own tissues. If one can correct the problems without prosthetic devices when they are young, a successful result should remain. If we use an artificial device, the likelihood of having to revise it or remove it is considerable if we follow the patient for many years.

As regards malignancy, there have been a few reports of patients with ileal loops and colon loops who have had tumors, but they are uncommon.

In contrast there is a 10% rate of late carcinoma in patients with ureterosigmoidostomy. It seems that the combination of urine and feces is much more likely to produce malignancy of bowel than urine alone. Crissey and Gittes showed that to be true in laboratory animals as well. We think that the long-term risk of carcinoma should not be particularly high in these patients with augmentation cystoplasty. I tell the patients that we don't know for certain the long-term answer to that question, but that it would seem reasonable to accept the risk when we are faced with either leaving them with a bag or using bowel to reconstruct their urinary tracts.

Finally I would like to say that all that I have presented has evolved from contributions of others through the years. We should pay special recognition to Dr. Eugene Bricker, who introduced the ileal loop in managing patients after pelvic exenteration. Another pioneer and member of this Association is Dr. Willard Goodwin, who demonstrated the use of ileum for ureter as well as for bladder augmentation. Without those milestone steps, much of today's reconstructive surgery would not exist.

The Process of Microbial Translocation

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The process of microbial translocation was studied using *Candida albicans*, *Escherichia coli*, or endotoxin instilled into Thiry-Vella loops of thermally injured guinea pigs and rats. Translocation of *C. albicans* occurred by direct penetration of enterocytes by a unique process different from classical phagocytosis. Translocation between enterocytes was not observed. Internalization was associated with a disturbance of the plasma membrane and brush border, but most internalized organisms were not surrounded by a plasma membrane. Passage of the candida into the lamina propria appeared to be associated with disruption of the basal membrane with extrusion of cytoplasm of the cell and candida. Organisms in the lamina propria were commonly phagocytized by macrophages but also were found free in lymphatics and blood vessels. Translocation of *E. coli* and endotoxin also occurred directly through enterocytes rather than between them, but translocated endotoxin diffused through the lamina propria and muscular wall of the bowel wall by passing between rather than through the myocytes. These descriptive phenomena provide new insight into the role of the enterocyte and intestinal immune cells in the translocation process.

BERG AND GARLINGTON[1] defined bacterial translocation as 'the passage of viable bacteria through the epithelial mucosa into the lamina propria and then to the mesenteric lymph nodes, and possibly other tissues.' This concept should be refined to include all microbial translocation, defined as the passage of both viable and nonviable microbes and microbial products such as endotoxin across an anatomically intact intestinal barrier.

Studies in several laboratories have shown that translocation, as measured by recovery of viable organisms from the regional lymph nodes, is increased by hemorrhagic shock,[2] antibiotic therapy,[3,4] intestinal obstruction,[5,6] parenterally administered endotoxin,[7] hyperpyrexia,[8] thermal injury,[9] intravenous feedings,[10] elemental diets,[11,12] and cytotoxic drugs,[13] but not by simple protein malnutrition[7] or T-cell depletion.[14] Translocation of bacteria is decreased by feeding complete enteral diets,[10] glutamine,[13,15] trophic hormones such as bombesin,[16] and prevention of intestinal ischemia.[17] Based on these observations, it has been postulated that increased rates of translocation increase the hypermetabolic response of injured and septic patients,[18] cause a septic state in surgical patients in the absence of a defined infectious focus,[19] and predispose or contribute to the development of multisystem organ failure.[20-22]

Few studies have evaluated how microbes pass through the intestinal barrier. Cole et al.[23] demonstrated direct candidal invasion of enterocytes after intragastric inoculation in immunologically immature 5- to 6-day-old mice, and Krause et al.[24] demonstrated in a bold clinical experiment that translocation occurred in a normal human following ingesting a large dose of *Candida albicans*. Deitch et al.[25] showed invasion of *Escherichia coli* in ulcerations of villus tips following hemorrhagic shock, and Wells et al.[26] more recently demonstrated that enterococci have a transmucosal route of translocation. In a previous

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study we showed rapid translocation of biotynilated *C. albicans* into the lamina propria through enterocytes.[27]

To better understand the process of microbial translocation, we have used three translocation 'probes' (viable *C. albicans*, viable *E. coli*, and partially purified endotoxin) to observe and document the anatomic process of translocation by light and electron microscopy. For this purpose a model was selected to achieve relatively high rates of translocation.

Materials and Methods

Animals and Animal Care

Female Hartley guinea pigs (Murphy Breeding Laboratory, Plainville, IL) weighing 350 to 450 g and male Lewis rats (Harlan Sprague Dawley Inc., Indianapolis, IN) weighing 225 to 250 g were used for these experiments. Animals were quarantined for 1 week in standard laboratory conditions so they could adapt to the environment and to exclude animals with pre-existing diseases. The experimental protocols were approved by the University of Cincinnati Medical Center Institutional Animal Care and Use Committee, and the animals were housed in an AAALAC-approved facility. In conducting the described research in this report, the investigators adhered to the Guide for the Care and Use of Laboratory Animals as set forth by the Committee on the Care and Use of Laboratory Animals, National Research Council, United States Department of Health and Human Services, National Institutes of Health.

Surgical Procedures and Burn Injuries

All operative procedures and potentially painful manipulations were performed under general anesthesia. Guinea pigs were anesthetized with intramuscular injection of 0.2 mg/kg of acetopromazine malate, 0.33 mg/kg, xylazine citrate, and 0.4 mg/kg atropine sulfate. Rats were anesthetized with 65 mg/kg sodium pentothal injected intraperitoneally.

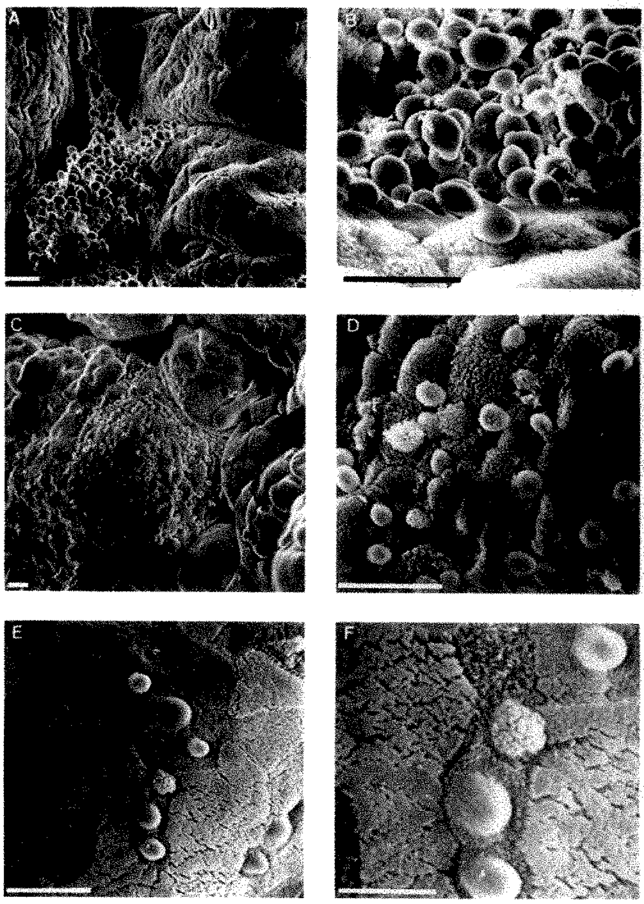
Thiry-Vella loops were created by proximal and distal enterostomy of a 10-cm loop of distal ileum containing at least one Peyer's patch. Bowel continuity was restored by end-to-end anastamosis using a running 6-0 Prolene^{R} suture, and the animals were allowed to recover for 7 to 10 days before experiments were performed.

Burn injury of 50% full-thickness total body surface area (TBSA) was inflicted under general anesthesia according to a previously described method.[27] After burn injury, intraperitoneal injection of 20 mL lactated Ringer's solution was administered for fluid resuscitation. The surface area of the guinea pig in square centimeters was calculated using the following formula: $-24.3 + 0.445 \times$ (weight in grams) $+ 10.2 \times$ (length in centimeters).[28] The formula of Horst et al.[29] was used for calculating the TBSA of the rat, *i.e.*, surface area in square centimeters equals $9.1 \times w^{2/3}$, where w equals body weight in grams.

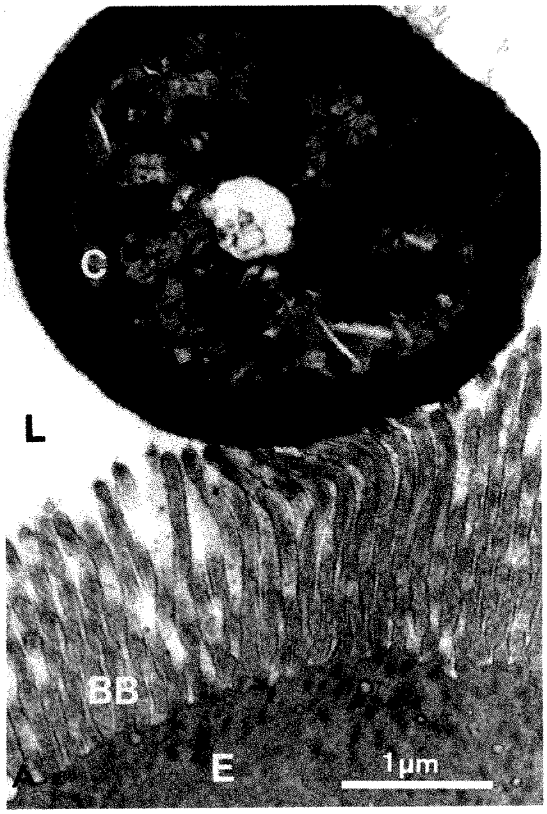
Preparation of the Microbial Probe

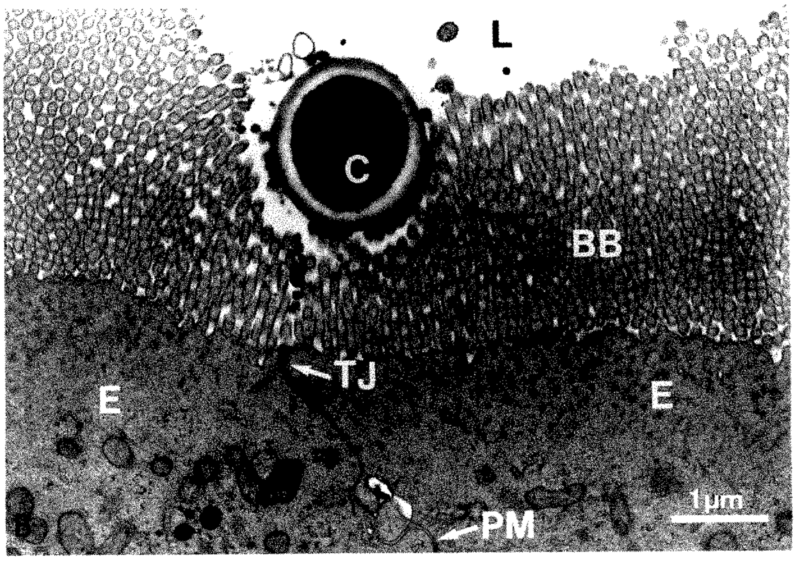
To provide a baseline for comparison with other experiments, the *E. coli* and endotoxin were labeled with ^{14}C glucose.

Preparation of C. albicans. A strain of *C. albicans* isolated from the blood of a burn patient at Shriners Burns Institute, Cincinnati, Ohio, was used for these experiments. This isolate was serotype A and biotype number 177, as characterized by a modified Odds and Abbott sys-

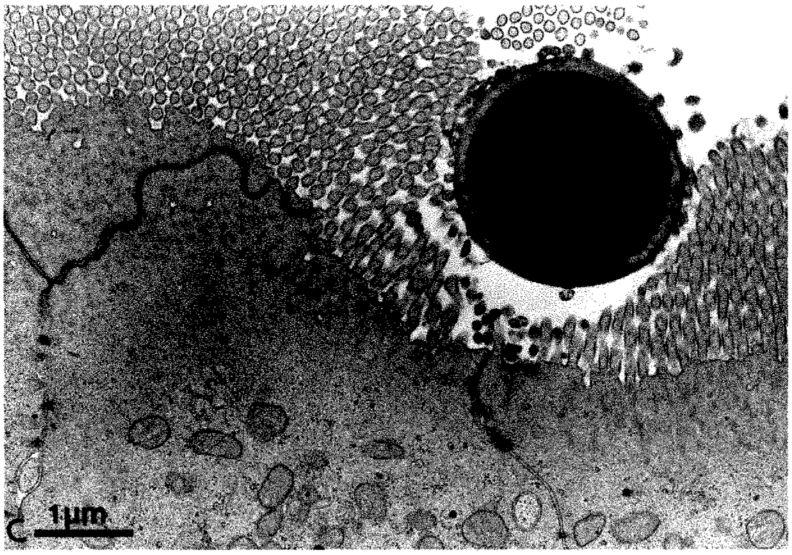


FIGS. 1A–F. Scanning electron micrographs of the mucosal surface of guinea pig Thiry-Vella loops instilled with *C. albicans*. (A and B) Specimens taken 1 hour after burn; (C–F) specimens taken 12 hours after burn. The scale bars on A to E are 10 μm and the scale for F is 5 μm. Note that in A and B there is already attachment of the candida to the epithelium, but many of the candida are entrapped by mucous. (C) Diffuse attachment to one of the villi but not to others as was characteristic throughout most of the sections examined. (D, E, and F) Varying degrees of penetration of the candida into the brush border.





FIGS. 2A–D. Transmission electron micrographs of the attachment of candida to the microvillus layer. (A) A candida is shown with attachment causing distortion of the outer portion of the microvillus layer. (B) A yeast form is seen penetrating into the brush border. Note that there is distortion of some of the microvilli suggesting enzymatic alteration. (C) Further penetration of a yeast form is seen with further distortion of the microvilli. (D) An engulfed yeast is seen with disorganization of the microvillus layer. At the upper part of the vacuole surrounding the candida are small circular structures that appear to be remnants of microvilli.



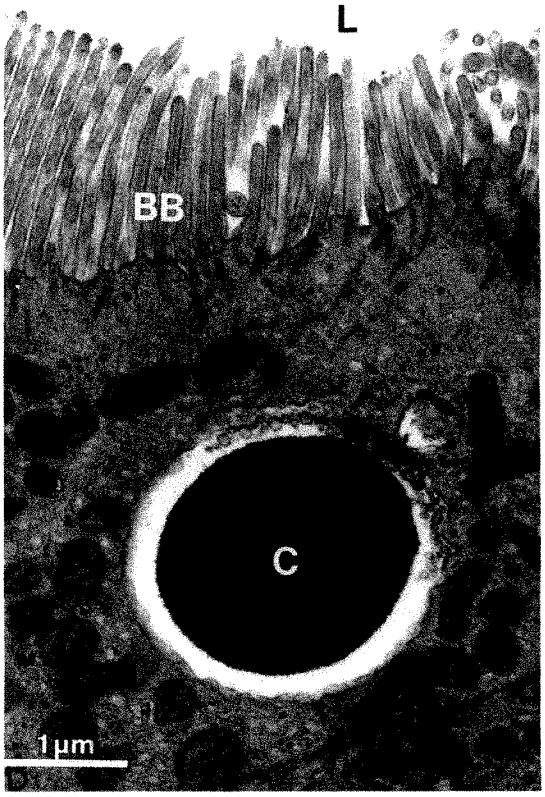


FIG. 2. (*Continued*)

tem.[30] Brain heart infusion broth was inoculated with *C. albicans* stock culture and allowed to grow in a shaking water bath at 37 C for approximately 17 hours. One half milliliter of this culture was plated onto Sabouraud dextrose agar and incubated at 37 C for 48 hours. The plates were maintained at 4 C for 3 to 10 days and scraped to collect the *C. albicans*. The organisms were suspended in phosphate-buffered saline (PBS), pelleted at 2000 rpm, and washed three additional times. The final pellet was suspended in PBS, counted using a hemocytometer, and viability was determined by trypan blue exclusion. Only preparations with more than 90% viability were used with the final concentration adjusted to approximately 1×10^{10} organisms/mL.

Preparation of ^{14}C-labeled E. coli. The *E. coli* strain used, obtained from Richard L. Simmons, M.D., University of Minnesota, Minneapolis, Minnesota, was grown in 75 mL of lipopolysaccharide (LPS) growth media (2.5 g/l peptone, 5 g/l NaCl, 2.5 g/l Na_2HPO_4) in a shaking water bath at 37 C for approximately 17 hours. This culture was used to inoculate 50 mL of fresh LPS media containing 500 μCi of ^{14}C glucose (specific activity 310 mCi/mmol, ICN Biomedicals Inc., Cleveland, OH), and then incubated for an additional 19 hours. The isotope-labeled bacteria were washed, resuspended in sterile saline, and adjusted to a final concentration of 1×10^{10} organisms/mL using a Klett densitomer (Klett Manufacturing Co., Long Island, NY).

Preparation of ^{14}C endotoxin. E. coli was inoculated into 50 mL of LPS growth media and incubated at 37 C in a shaking water bath for approximately 17 hours. This culture was then added to 2 L of LPS growth media containing 1 mCi of ^{14}C glucose and incubated at 37 C as above for an additional 27 hours. The media were then centrifuged at 6500*g* for 10 minutes at 4 C, the pellet was resuspended in 40 mL of distilled H_2O and centrifuged at 2000 rpm for 10 minutes. This pellet was washed in the same manner with 40 mL of absolute ethyl alcohol and then 40 mL of acetone. The final pellet was frozen at −70 C for 1 hour and then lyophilized overnight to dehydrate. The LPS was extracted with 1.5 mL of phenol extraction solution (13% phenol, 33% chloroform, and 54% petroleum ether) and sonicated for 15 minutes until the pellet was completely resuspended. The suspension was then centrifuged at 1000*g* for 15 minutes at 4 C and the supernatant poured through #3 Whatman filter paper into a polypropylene tube, frozen, and lyophilized overnight. Distilled water was added drop by drop to solubilize the phenol and the labeled LPS was collected by centrifugation at 2000*g* for 10 minutes, frozen at −70 C, and lyophilized for storage at −70 C until use.

Experimental Procedure

Either *C. albicans* 10^{10} in 1 mL PBS, *E. coli* 10^{10} in 1 mL, or endotoxin (1 mg in 1 mL) was instilled into the

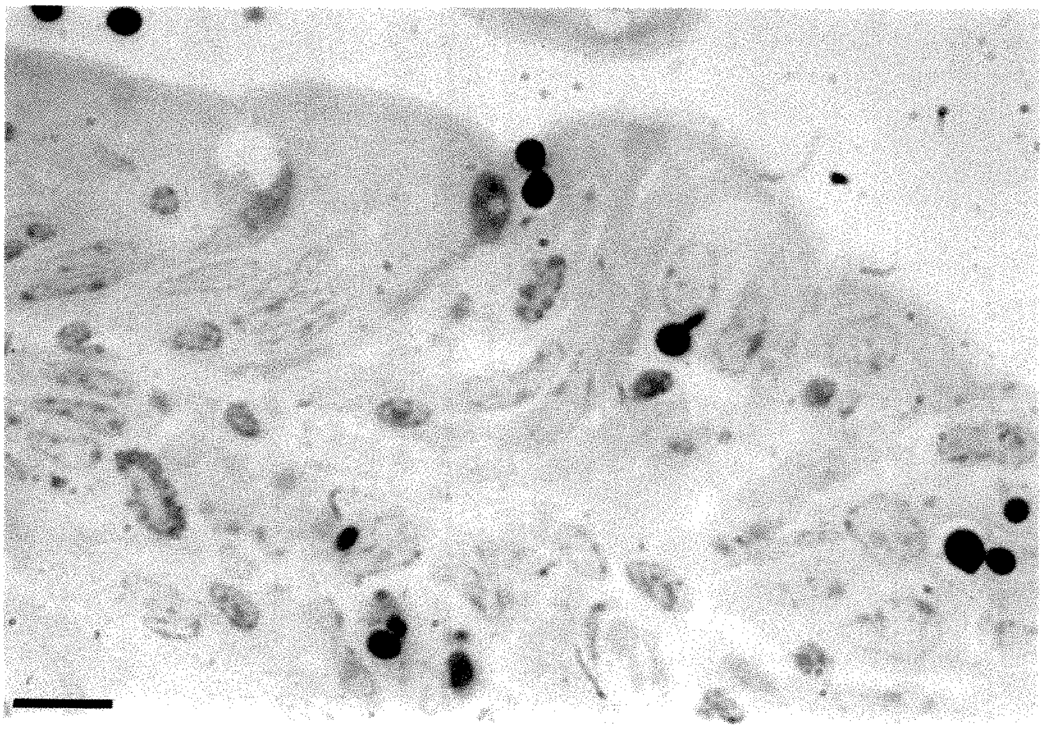


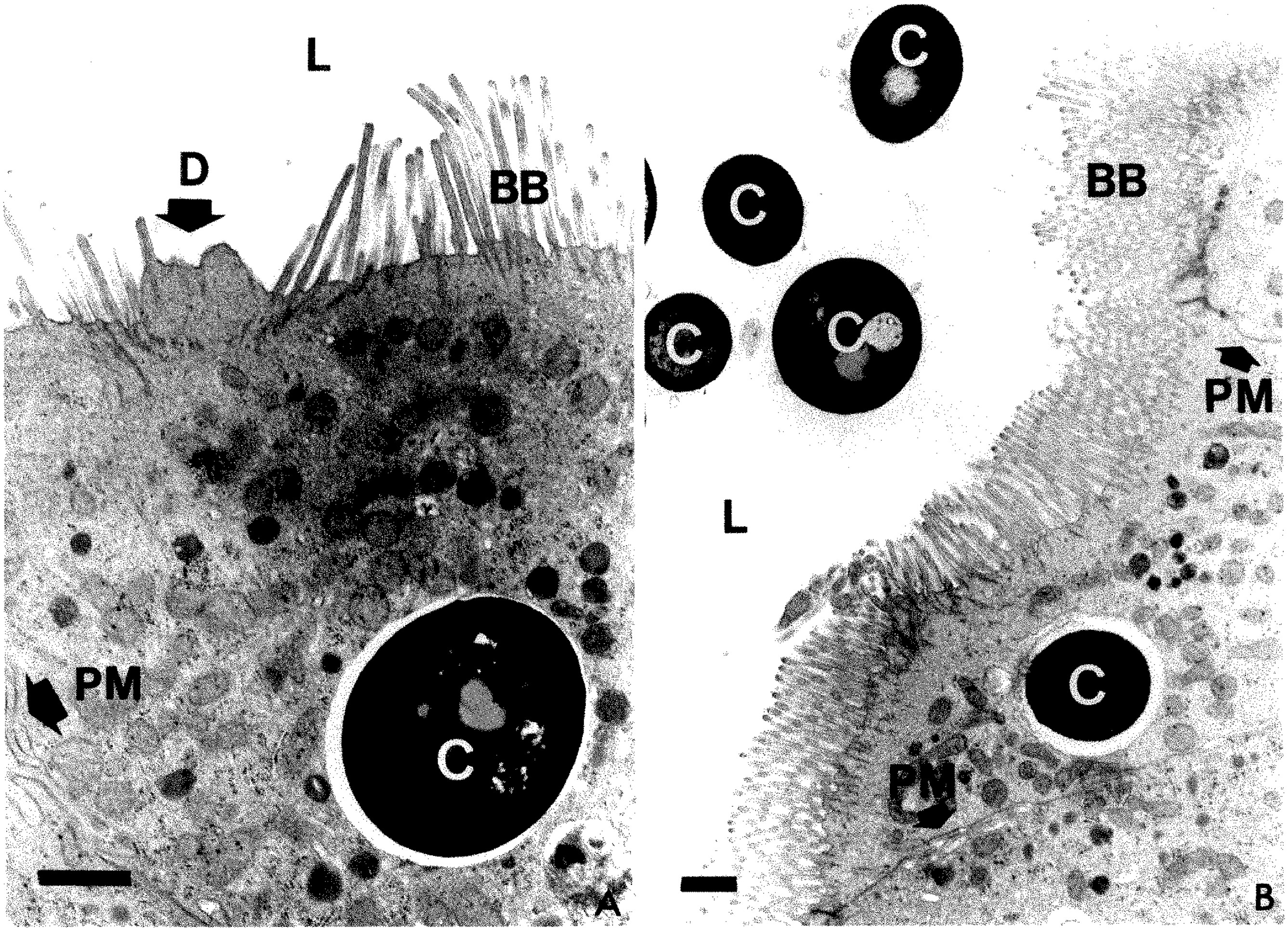
FIG. 3. Light micrograph of the guinea pig ileum stained with toluidine blue. Many candidal bodies are seen within mucosal cells, one budding in a subnuclear region. Note especially the penetration of two candida through the brush border in the central portion of the picture (scale bar = 10 μm).

proximal limb of the Thiry-Vella loop after anesthesia but before the time of burn injury. Eight guinea pigs and eight rats were used for each translocation 'probe,' 48 in all. In some animals the Thiry-Vella loop first was irrigated with saline to remove excess mucous within the loop. The distal end was closed with an encircling ligature and the proximal end was similarly closed after instillation of the translocation probe to prevent its discharge. Animals were killed at 1, 4, and 24 hours in most experiments and at 2 and 6 hours in other experiments. When the animals were killed the Thiry-Vella loops were excised and sections taken from the intestine both in areas with and without Peyer's patches. These were frozen with dry ice or placed in a fixative composed of 2% glutaraldehyde and 2% paraformaldehyde in 0.1 mol/L (molar) sodium cacodylate buffer with 50 mg/L calcium chloride. In some experiments tissue was taken for frozen sections to be processed for fluorescent labeling studies, and the remaining loop filled with fixative before taking the sections.

Microscopic Examinations

Preparation of samples for microscopy. Fixed tissue for light microscopy (LM) and transmission electron microscopy (TEM) was washed in 0.1 mol/L sodium cacodylate with 10% sucrose and postfixed with 1% osmium tetroxide in the same buffer. The tissue was washed, dehydrated to 100% ethanol, exchanged into propylene oxide, and embedded in Medcast-Araldite resin (Ted Pella, Inc., Tustin, CA).

Polymerized blocks were sectioned with a Reichert-Jung Ultracut E ultramicrotome (Cambridge Instruments, Inc., Buffalo, NY). For light microscopy, semithin sections (~1 μm) were cut and mounted on chromalum gelatin-



FIGS. 4A and B. These TEMs show gross distortion of the plasma membrane and brush border at presumed sites of entry into the enterocyte. (A) Also note lack of a membrane around the candida. (B) This and all other candida within the epithelial layer clearly are seen to be within enterocytes rather than between them. Also note the membranous fragments at the outer portion of the vacuole (scale bars = 1 μm).

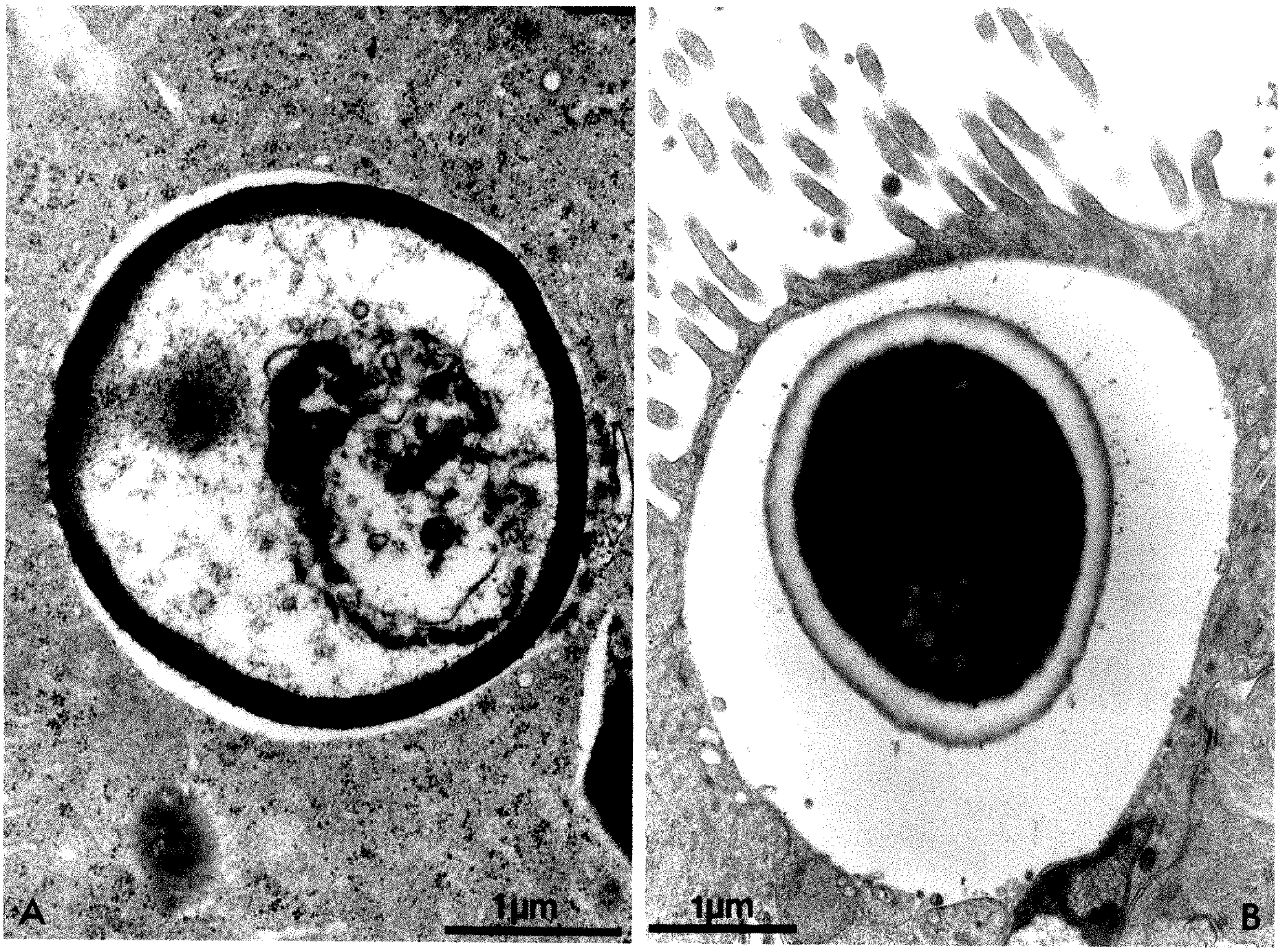
coated slides. Semithin sections subsequently were stained with toluidine blue and covered with cover slips using Permount^R. Thin sections for TEM were mounted on uncoated 200 mesh copper grids and stained with uranyl acetate and lead citrate solutions.

Fixed tissue for scanning electron microscopy (SEM) was washed in osmotically balanced 0.1 mol/L sodium cacodylate, postfixed in 1% osmium tetroxide in the same buffer, rewashed, and dehydrated to absolute ethanol. Exchange to liquid carbon dioxide and critical point drying were accomplished in a DCP-1 Critical Point Dryer (Denton Vacuum, Inc., Cherry Hill, NJ). Dried specimens were mounted on aluminum stubs and coated with gold-palladium in a Fullam Mini-coater (Ernest F. Fullam, Inc., Lathan, NY).

Examination by light microscopy. The semithin sections stained with toluidine blue were examined by standard LM using magnification up to 1000x. Photographs were made using Kodak Ektachrome 160 Tungsten light film (Kodak, Rochester, NY) at magnifications of 80x and 320x.

TEM and SEM. Transmission electron microscopic observation was accomplished with a JEOL JEM-100C microscope (JEOL Ltd., Boston, MA). Micrography was performed using Kodak electron microscope film 4489. Scanning electron microscopic observation was accomplished with a JEOL JSM-35 microscope and images were recorded onto Polaroid type 55 positive/negative sheet film.

Preparation of monoclonal antibody 2G10. Monoclonal antibody 2G10 was made against the LPS of *E. coli* and *Salmonella minnesota* by the method described by Priest et al.[31] Monoclonal antibody subisotype determination demonstrated that 2G10 was of the IgG_1 subclass. Monoclonal antibody 2G10 bound strongly by Western immunotransblot analysis to *S. minnesota* Ra, Rb, Rc, Rd,



FIGS. 5A–B. Most of the internalized candida were not surrounded by a membranous structure, suggesting that internalization occurred by a process other than classical phagocytosis.

Re, and wild type, *Salmonella typhimurium, E. coli* J5, *E. coli* 0111:B4, and *E. coli* 055:B5. This binding pattern was most compatible with outer/intermediate core region binding and was highly cross-reactive. The enzyme-linked immunoabsorbant assay demonstrated elevated titers against *S. minnesota* Re and *E. coli* J5 LPS and minimal binding against all other types of LPS.

Fluorescence microscropy. Frozen sections on slides were warmed at 70 C for 2 minutes, immersed in cold acetone for 10 minutes, and allowed to air dry. The tissue was then rehydrated in PBS pH 7.4 for 2 minutes, excess PBS was removed, and PBS plus 5% goat serum was added and the slides were incubated for 1 hour at 37 C. After incubation the slides were washed for 5 minutes in PBS and mouse anti-LPS (2G10, 1:40 in PBS + 5% goat serum, described above) was added, and the slides were incubated for 2 hours at 37 C. Following three 10-minute washes in PBS, goat anti-mouse antibody labeled with fluorescein isothiocyanate (FITC) [1:7 in PBS + 0.1% bovine serum albumin (BSA)] (Kierkegaard and Perry, Gaithersburg, MD) was added and the slides were incubated again at 37 C for 2 hours. Following a rinse in PBS, a solution of propidium iodide (500 ng/mL in PBS) was added for 5 minutes and the slides were washed, allowed to dry, and covered with cover slips.

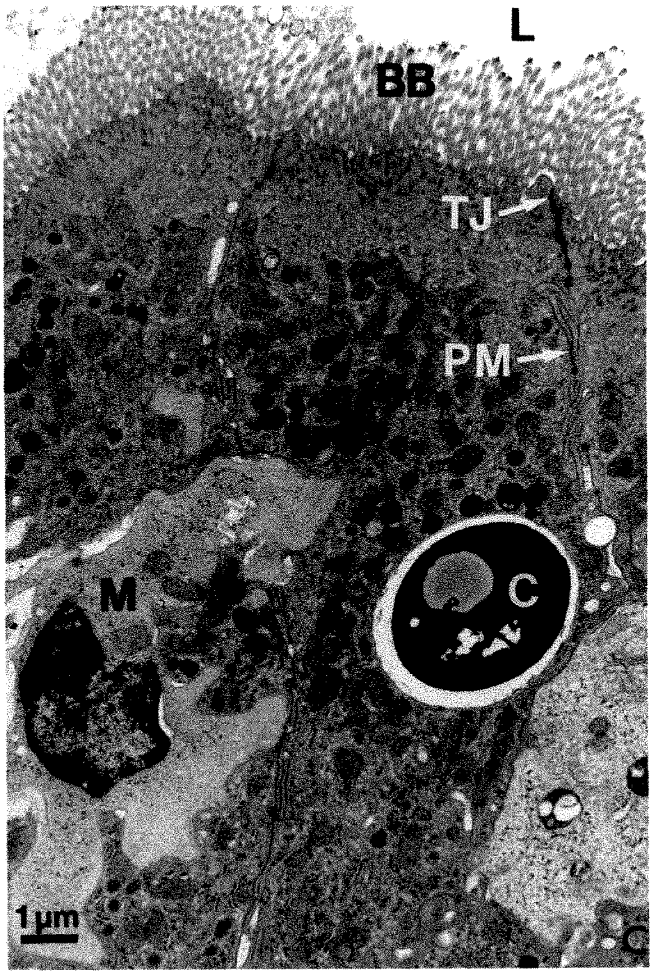


FIG. 5C. An enterocyte containing a candida is bordered on both sides by intraepithelial macrophages migrating through the mucosa *via* the intercellular junctions.

Results

Studies with C. Albicans

Specimens from the rats and guinea pigs provided virtually identical examples and will be discussed together. More than 100 semithin sections stained with toluidine blue were examined by LM, and specimens of special interest were sectioned further for study by TEM. A characteristic appearance of *C. albicans* by LM when stained with toluidine blue as well as a typical appearance by TEM and the presence of pathognomonic budding yeast in many specimens provided easy and sure identification in most specimens.

Translocation directly into the mucosal cells was seen to occur as early as 1 hour after burn. Translocation of candida into the enterocytes was more frequently observed at the villus tips, sometimes associated with submucosal edema. In some specimens there was apparent edema between the epithelial cells but candida were never seen to translocate into these edematous spaces or between cells. Only rarely was there frank ulceration of the villus tips with candidal invasion through the ulcerations. Examination of different specimens from the same animal that showed translocation did not occur uniformly. This variability appeared in some instances to occur because of a lack of access of the organisms to the mucosal surface because of a blanket of mucous. In later experiments attempts were made to remove some of the mucous layer by gentle irrigation of the loop with saline before instillation of the candida, and this promoted a more even distribution of translocation. Even so translocation was seen to occur extensively in villi adjacent to other villi in which no translocation occurred.

Observations of the translocation process. By SEM contact of individual candida with attachment to the brush border was readily observed (Fig. 1). After internalization, the organisms appeared as hemispherical irregularities of the surface. Transmission electron microscopy showed some erosion of the tips of the microvilli, with disorientation of their linear alignment followed by penetration of the organism into the brush border (Fig. 2). Many organisms were seen associated with the brush border and many organisms were seen within the enterocytes immediately below the plasma membrane, but the actual process of internalization was observed only once (by LM) (Fig. 3), indicating that the internalization occurred rapidly. Considerable disturbance of the plasma membrane was seen by TEM at sites of entry (Fig. 4), which could represent loss of continuity of the actin filament network within the brush border. Internalized organisms were contained within vacuoles that were rarely lined by membrane with no evidence of lysosomal degranulation (Fig. 5). Sometimes more than one candida were seen within an individual enterocyte, and they were found throughout the apical to basal orientations of the cells. Passage through the basal side of the cell also appeared to be a rapid process and was infrequently observed. However, in one specimen, candida appeared to be extruded into the lamina propria through a disruption of the basement membrane carrying along with them portions of the cytoplasm and intracellular organelles (Fig. 6). In this example the disruption may represent local perforation of the plasma membrane allowing release of candida. Morphologically enterocytes appeared otherwise uninjured by this process of transport.

Many candida were found in the lamina propria, indicating that residence there was relatively prolonged. Most of the organisms were found near the villus tips or in the middle of the villi, with only a few at the base, suggesting an orderly egress from this anatomic position. By both LM and TEM, most organisms were engulfed by phagocytic cells, predominately macrophages. Macrophages were encountered that had ingested several candida, and candida were observed in different states of degradation. However in many specimens candida were found to be budding both within macrophages and in the extracellular spaces. Perhaps 20% to 30% were within extracellular spaces, many of these free within lymphatics (Fig. 7a) or less frequently in veinules (Fig. 7b) In the submucosal lymphatics, the organisms were found both free and within macrophages, sometimes associated with leukocyte aggregates.

Examples were seen in which a high frequency of translocation occurred through the mucosal epithelium covering Peyer's patches. Organisms were seen throughout the structure of the Peyer's patch and appeared to move into the germinal centers through the pericortical tissue. Macrophages within the germinal centers had many inclusions with the microscopic appearance of degrading candida. However similar structures also were seen in germinal center macrophages in animals not injected with candida. Nevertheless the presence of budding yeast cells within germinal center macrophages, found in several

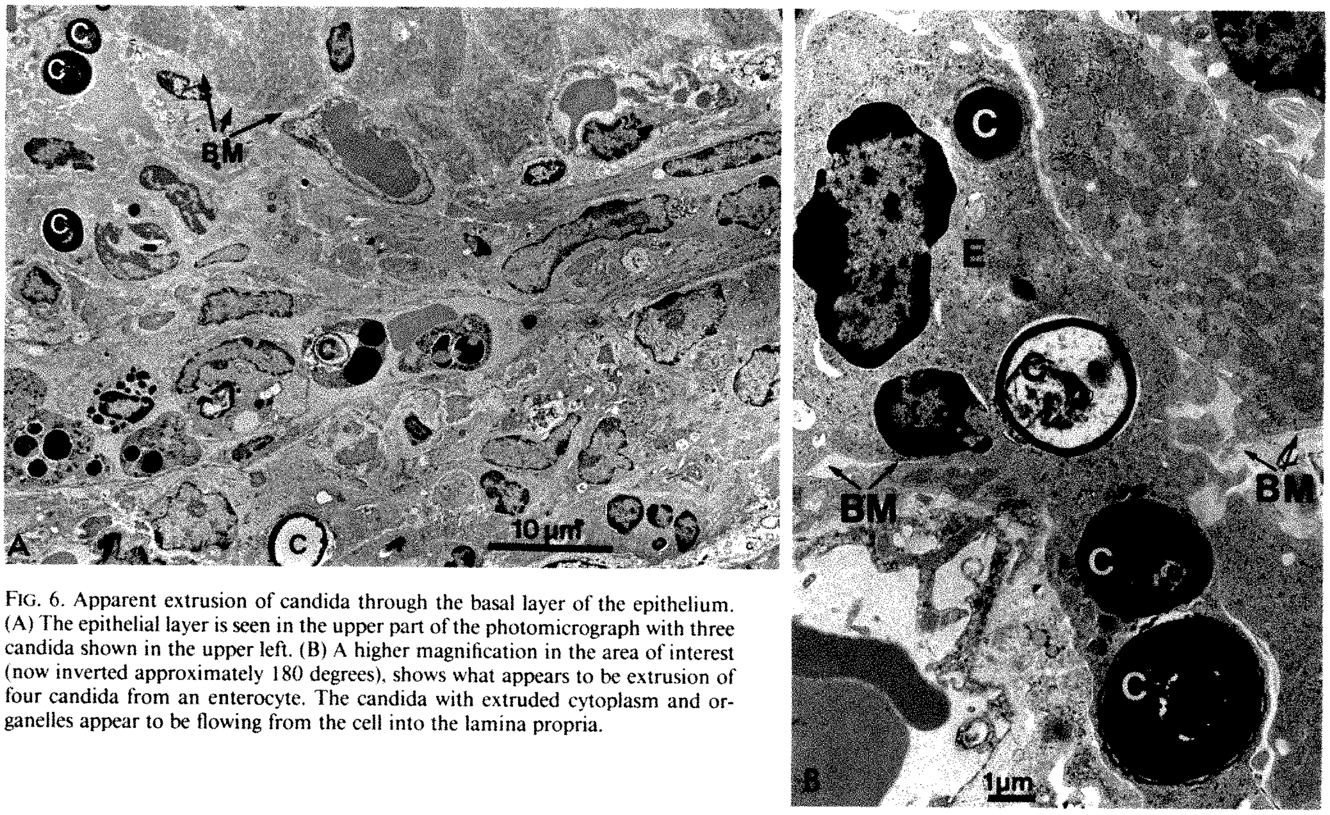
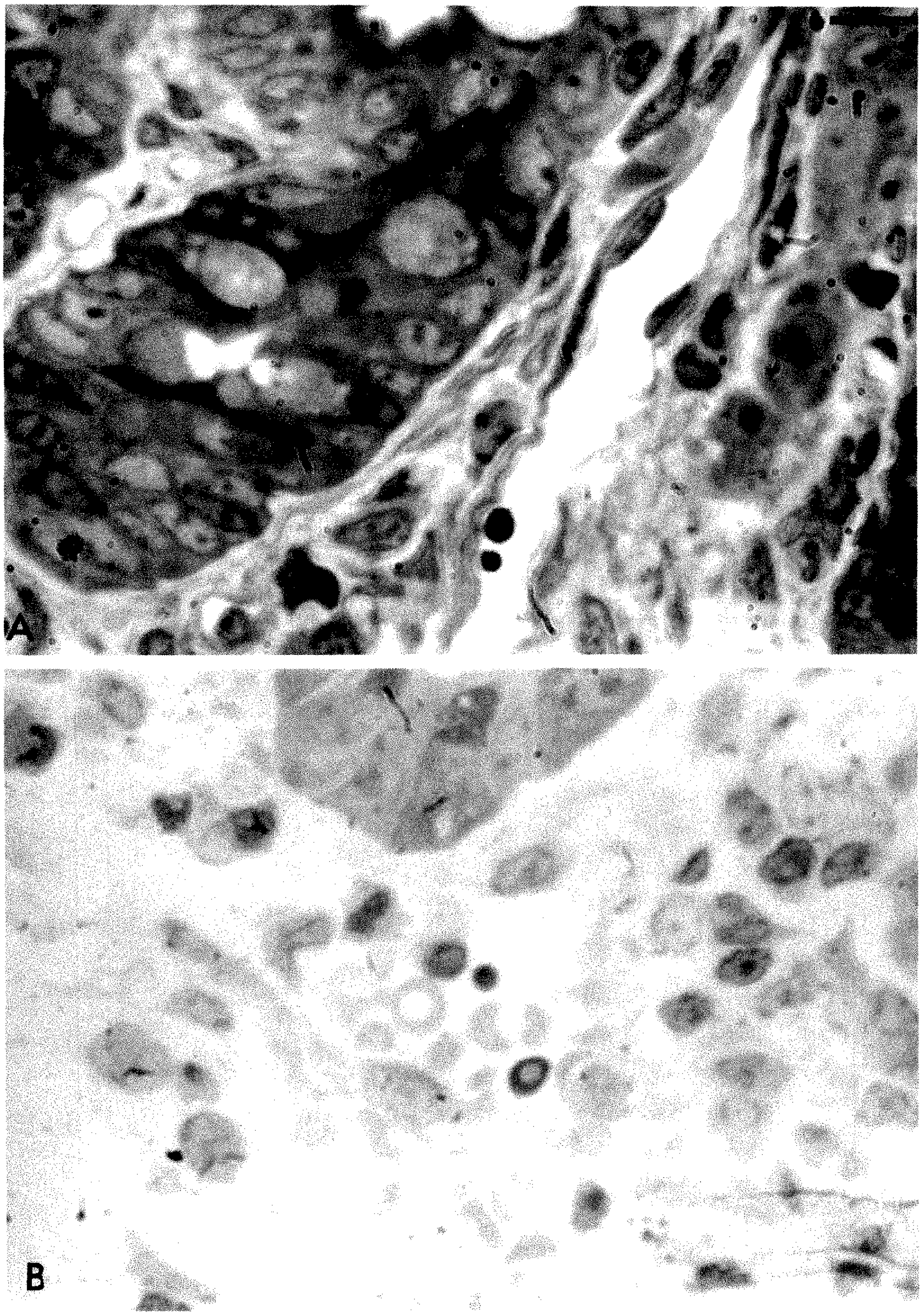


FIG. 6. Apparent extrusion of candida through the basal layer of the epithelium. (A) The epithelial layer is seen in the upper part of the photomicrograph with three candida shown in the upper left. (B) A higher magnification in the area of interest (now inverted approximately 180 degrees), shows what appears to be extrusion of four candida from an enterocyte. The candida with extruded cytoplasm and organelles appear to be flowing from the cell into the lamina propria.



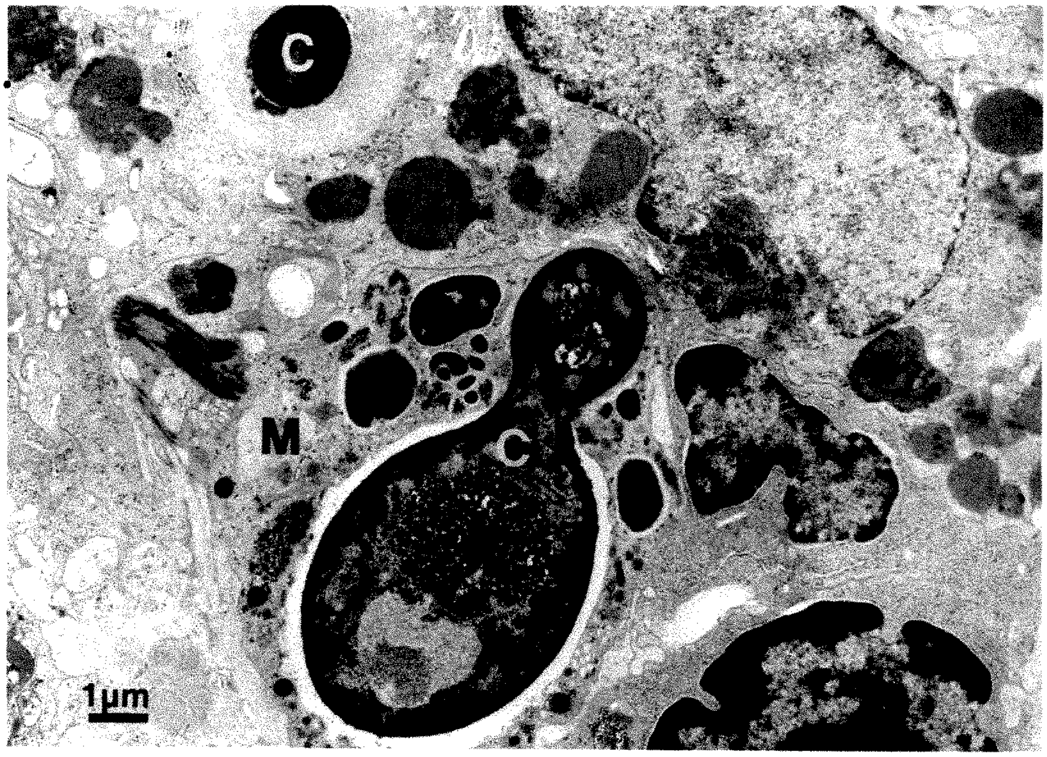
FIGS. 7A and B. Light micrographs stained with toluidine blue. (A) Three candidal organisms are seen within lymphatics of the lamina propria (2) and submucosa (1) without evidence of phagocytosis. (B) Two candida are found within a small venule at the base of the lamina propria without evidence of phagocytosis (scale bars = 10 μm).

specimens (Fig. 8), indicated that the germinal centers might be an active site of degradation for candida along with other potential pathogens and effete host cells.

The regional lymph nodes showed candida less frequently than the mucosal cells and lamina propria. When yeast bodies were found, they were both free in lymphatics and engulfed by macrophages throughout the nodes (Fig. 9).

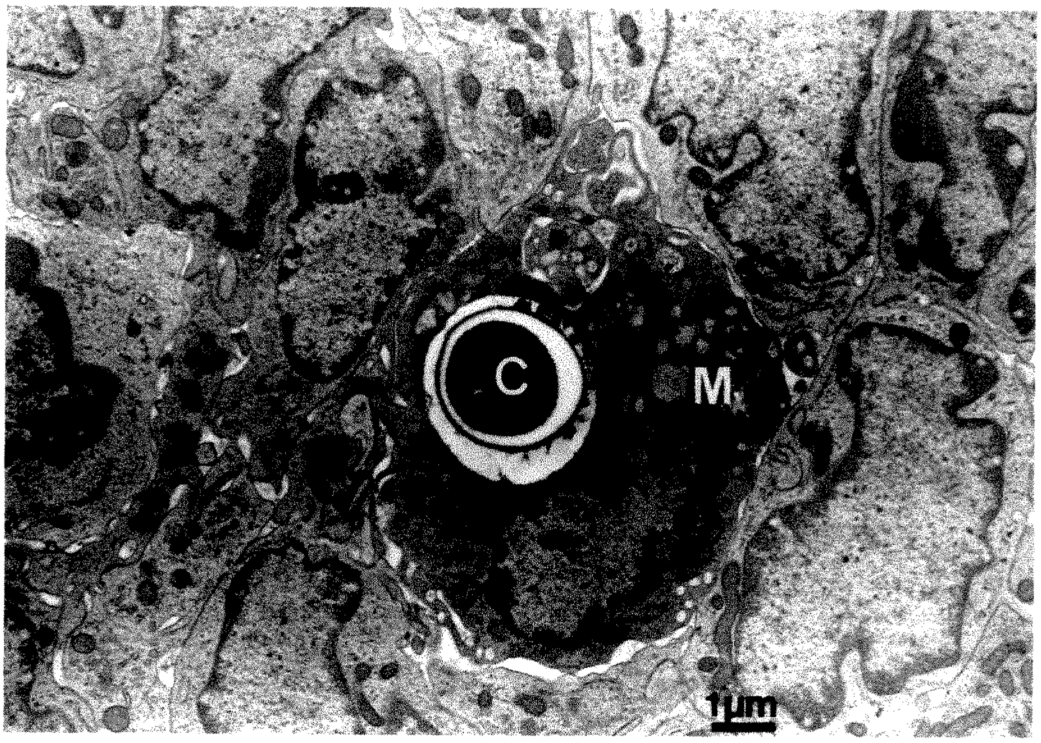
In specimens taken 24 hours after intraluminal infusion of the yeast, there were fewer numbers within the entero-

FIG. 8. Budding yeast within a macrophage in a germinal center of a Peyer's patch.



cytes and the lamina propria. However microabscesses with budding yeast were found in the lamina propria (Fig. 10), and vascular occlusion by budding yeast was found in some of the large vessels. Of interest was the presence of yeast on the serosal surface of the intestine with invasion into the muscular layer. Rarely, in specimens examined from animals killed closer to the time of the burn, were yeast forms found within the muscular wall.

FIG. 9. Candida within a macrophage in the pericorticol area of a mesenteric lymph node.



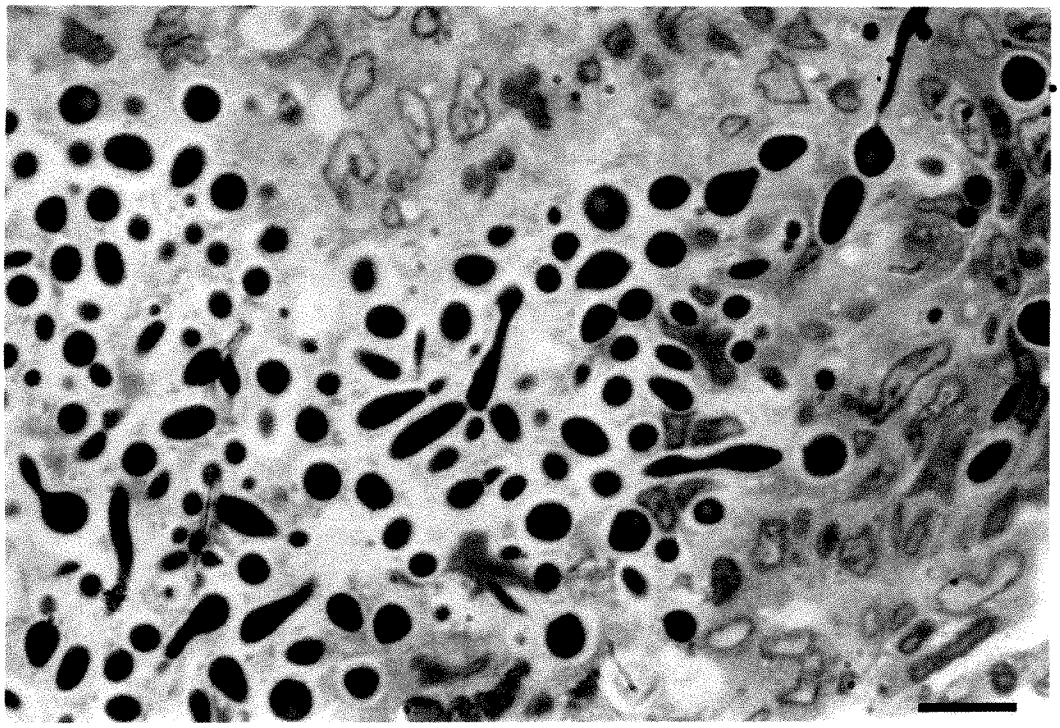


FIG. 10. Light micrograph of a small microabscess with budding candida in the lamina propria of a rat 24 hours after instillation of candida into the loop. The mucosa was intact over the microabscess (scale bar = 10 μm).

E. coli

Study of translocation of *E. coli* in Thiry-Vella loops by light microscopy failed to provide sufficient resolution to accurately trace the process. Because of this it was difficult to accurately select areas for thin-section processing. Nevertheless, using TEM, several organisms were seen embedded in the brush border as well as within the cytoplasm (not shown). Like candida the *E. coli* was always within the enterocytes and never was seen passing between them.

Examination of frozen sections of tissue stained by a fluorescent antibody technique using a lipopolysaccharide-specific monoclonal antibody revealed that the translocation process for *E. coli* was both similar to and different from that of *C. albicans.* This difference arose because fluorescent staining occurred not only of the infused, intact live organisms but also of live resident *E. coli*, infused and resident dead *E. coli*, and endotoxin that was free from bacterial cells.

Within 1 hour granular staining was prominent within the enterocytes, the granules being both quite small and the size of the *E. coli* organism itself (Fig. 11). Clumping and aggregation of these particles became more prominent in the lamina propria with beginning concentration within cells, presumably macrophages. The relative numbers of stained cells and their density increased as the bottom of the lamina propria was approached. Stained cells as well as free fluorescent particles were readily demonstrable within the submucosa but insufficient resolution was not possible on frozen sections to determine whether the stained particles were largely within vascular structures or outside them. A remarkable feature was that the specific granular stain was seen to extend throughout the muscular layers to the serosa, concentrating between rather than in cells.

The above observations were interpreted to show that both *E. coli* and its endotoxin product, which were identified by the lipopolysaccharide-specific monoclonal antibody, pass into the lamina propria directly through enterocytes in a manner similar to the larger *C. albicans* and not through the intercellular spaces. Once within the lamina propria, the *E. coli* and endotoxin appeared to be both free and cell bound, presumably to phagocytic mac-

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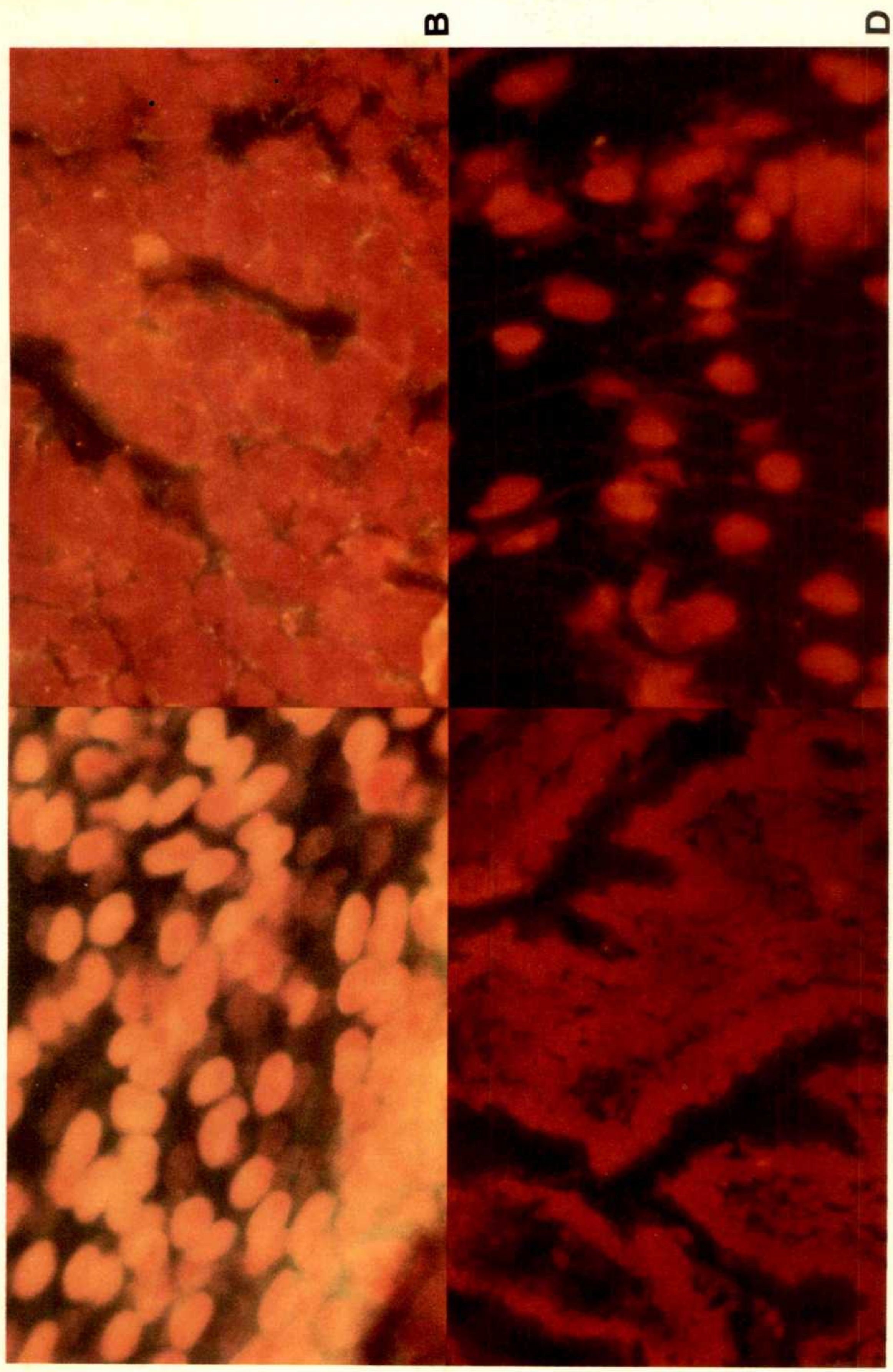
FIGS. 11A–E. (A) *Top left.* Immunofluorescent stain of a villus 1 hour after burn injury and instillation of *E. coli.* Note both diffuse and granular stains within both the mucosal layer and lamina propria. Some of the granular stain is located within macrophages. (B) *Top right.* Negative control, not treated with the anti-lipopolysaccharide monoclonal antibody, of a villus from the same animal. (C) *Bottom left.* There is increased localization of stain within phagocytic cells in the lamina propria. (D) *Bottom right.* The muscular layer of the intestine 2 hours after burn shows heavy specific staining for endotoxin in a granular pattern with apparent localization between the cells. (E) Page 509, *top left.* Negative control not stained with the anti-LPS antibody.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rophages. As the *E. coli* and endotoxin passed through the lamina propria, there was increasing concentration in cells, but there also was a considerable diffusion directly through the intercellular spaces of the muscular wall to reach the serosal surface.

Endotoxin

Samples to examine the translocation of endotoxin by fluorescence microscopy were processed in exactly the same manner as were samples for *E. coli*, and the findings were similar, with the exception that the stain within the enterocytes was more diffuse than granular (Fig. 12). Once inside the lamina propria, the endotoxin was concentrated within cells, presumably macrophages, and also spread diffusely throughout the intercellular spaces into and through the muscular wall, passing between the myocytes.

Discussion

Several factors are known to lead to increased translocation of microbes across the intestinal barrier.[32] These include (1) direct injury to the enterocytes, as may occur with gamma irradiation or toxins; (2) reduced blood flow to the intestine, as may occur with hemorrhagic shock or the systemic administration of endotoxin or inflammatory agents; (3) an increase in the microbial load, as may occur with resistant organisms following the use of antibiotics or antacids; and (4) altered nutrition, as may occur with the administration of defined elemental enteral diets or intravenous hyperalimentation. Particle size also may influence the rate of translocation, with smaller particles translocating more easily.

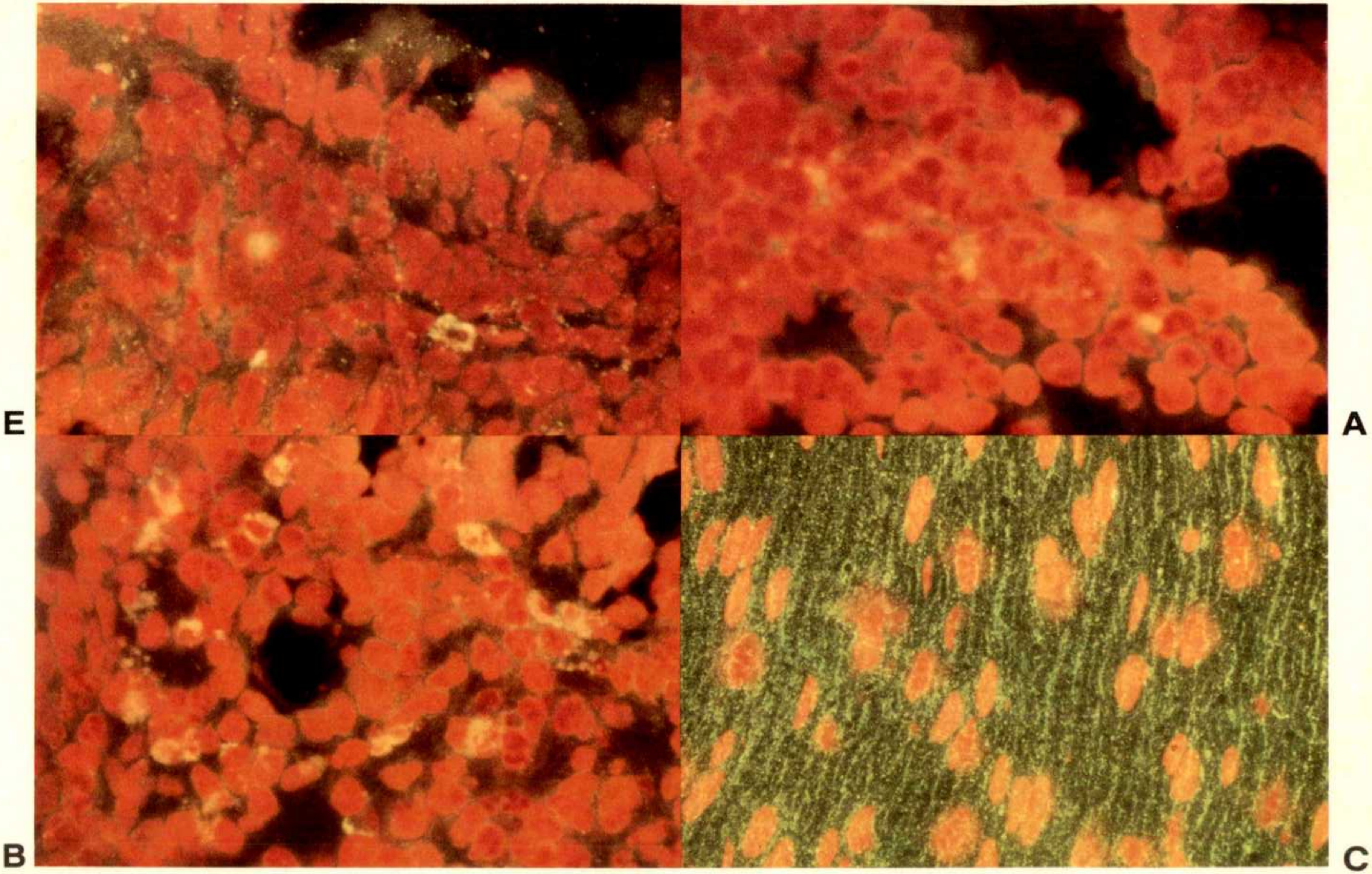
In this study we used a model that was associated with a relatively high rate of translocation. In the isolated Thiry-Vella loop, lack of luminal nutrients is associated with atrophy of the mucosa, even in well-nourished animals. However Deitch et al.[7] have shown that malnutrition with mucosal atrophy in itself will not necessarily result in an increase in translocation of bacteria. Use of a 50% burn coupled with a high concentration of microbes within the lumen of the Thiry-Vella loop was associated with a high rate of translocation, which, at least in the case of *C. albicans*, occurred by precisely the same mechanisms as were observed in intact gastrointestinal tracts of animals receiving thermal injury with or without antibiotics (unpublished observations).

The most important finding of our study is that both large (*C. albicans*) and small (*E. coli*) intact microbes and endotoxin translocated directly through morphologically intact enterocytes through a similar mechanism, which is different from classical phagocytosis and exocytosis. Translocation through rather than between enterocytes is consistent with the previous observations of Cole et al.,[23] who demonstrated direct internalization of candida by enterocytes after intragastric inoculation into 5- to 6-day-old mice and also the recent study of Wells et al.,[26] who showed that enterococci translocated through rather than between enterocytes in mice. These studies are remarkable in that endotoxin and perhaps some intact organisms once in the lamina propria pass between cells and through the muscular layer of the bowel to the serosa. This finding is consistent with the observations of Wells et al.,[33] who showed translocation of enteric bacteria through the intestinal wall into experimental intraperitoneal abscesses, and Papa et al.,[34] who demonstrated transmural migration of endotoxin through ischemic colons in dogs.

The observation that large amounts of endotoxin translocated across the mucosa is also an important finding. The usual method for quantitation of microbial translocation in experimental models is by enumerating culturable organisms in the mesenteric lymph nodes or other organs, but clearly this does not accurately reflect what has passed the intestinal barrier. The use of monoclonal antibodies as a semiquantitative marker for this process provides a more meaningful assessment for endotoxin. In an unpublished study using ^{14}C-labeled *E. coli*, infused into the gastrointestinal tract of mice, we showed that less than 0.1% of the radioactive label localizing in the mesenteric lymph nodes and the spleen was associated with viable bacteria when the animals were killed 1 to 4 hours after a 30% thermal injury. In this model, as well as the model with the Thiry-Vella loop, translocation was found to occur early, less than 1 hour after injury.

We showed that early feeding after burn injury decreases translocation in animals,[35] dampens the hypermetabolic response, and preserves intestinal morphology.[18] This suggests that abnormally high rates of translocation may be relatively easy to control by nutritional therapy after injury. Endotoxin from the gut has been shown to cause hepatic dysfunction and activation of Kupffer cells,[36] and many investigators think that continued microbial translocation in injured or critically ill patients provides the

FIGS. 12A–C. Specific stain for endotoxin using anti-LPS antibody in the ileum 1 hour after burn of an animal that received endotoxin in the Thiry-Vella loop. (A) *Top right.* There is diffuse staining of the cytoplasm of the enterocytes as well as the lamina propria. (B) *Bottom left.* Negative control without LPS antibody. (C) *Bottom right.* Specific anti-LPS immunofluorescent staining in the muscular wall is localized between rather than within the myocytes.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stimulus for a 'septic state,' even in the absence of a demonstrable focus of infection or bacteremia, and that this ultimately leads to the development of multiple-system organ failure.[19–22] While the current studies do not directly address the persistent question of clinical relevance of translocation, they provide clear evidence that translocation of viable microbes and endotoxin occurs with great frequency through morphologically intact enterocytes. Further investigation of the mechanisms regulating enterocyte function should lead to a better understanding of how to control the translocation process and better assess its role in the pathophysiology of human disease.

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DISCUSSION

DR. DAVID N. HERNDON (Galveston, Texas): There are still lingering doubts on the part of many as to the real physiologic significance of the phenomenon of translocation. The model demonstrated here is quite a severe one, a closed loop obstruction that would not surprise any of us to cause translocation. Clinically we surely see translocation in closed loop obstructions.

The first question would be: What is the true clinical relevance of this? We see this phenomenon in experimental animal models 48 hours after burn injury having migration of organisms to spleen, liver, and lung, but rarely in the human situation do we see sepsis in burn patients at 48 hours after injury.

The other extension of these clinical questions is that our most prominent pathogens in the lung, which are being proposed to come from bacterial translocation, are *enterococcus Klebsiella,* and *Staphylococcus.* What evidence can Dr. Alexander bring to us to show that these more commonly present pathogens in the human situation translocate from the GI tract?

DR. RICHARD SIMMONS (Pittsburgh, Pennsylvania): As usual Dr. Alexander has presented a brilliant, innovative approach to this problem. It is especially great because I agree with all his findings.

We have been working in this field for a number of years with Carol Wells from Minnesota and with Marc Rowe, Sam Smith, and Edna Mora in Pittsburgh. In a trip to the Beth Israel Hospital in Boston, Bill Silen and Mike Steer showed me this ussing chamber. The ussing chamber apparently is the standard method for studying electrolyte transport across the bowel. You simply open the bowel up and suspend it as a disk of bowel, which then is perfused on the mucosal and submucosal side simultaneously with oxygenated fluid.

If you use latex beads, which have no penetrating power and no enzymatic activity on the mucosal side of this *in vitro* model, the beads are taken up and enter into the enterocytes just the way the *Candida* seems to. The beads simply pass through the mucosal cells and drop out the other side, where they are phagocytosed by macrophages.

This is a normal bowel. First I would like to ask Wes whether he observed *Candida* translocating in normal animals as well as in burned animals.

Second this seems to be at least a two-stage process. In the first stage the enterocyte takes up or is penetrated by the microbe. The microbe passes through the cell and out the other side. Then, in the second stage, it is taken up by the macrophage.

I presume a third stage occurs in which the microbe is killed by the macrophage, and Wes showed nicely that sometimes killing takes place.

Now in the stress model studied so beautifully by Ed Deitch, there is usually some damage to the mucosa. But translocation also occurs in normal mucosa.

Does stress increase the ability or the tendency of the enterocyte to take up the particle, or is translocation increased in this system under stress because the macrophage is downregulated and cannot kill the organism as well?

DR. COURNEY TOWNSEND (Galveston, Texas): I also have questions about the model. That is, the removal of a piece of gut from the intact intestinal stream. We know food-stuffs are important not only for maintenance of structure but also for functional integrity of gut mucosa. Mark Evers in our laboratory has shown that the tophic effect of neurotensin, the only hormone to date, demonstrated to be effective in producing gut mucosa hyperplasia in a bypassed segment of gut, is less effective in the bypassed segment than in the incontinuity gut.

In addition to structural abnormalities or atrophy associated with fasting or with bypassed segments, there are also functional abnormalities, so my question relates to the function of the bypassed loop does the model relate, therefore, to the intact gut?

Functional abnormalities associated with atrophy include abnormalities of brush-border enzymes. Do you have any information about the functional properties of these mucosal cells that appear to be morphologically intact? Specifically what about immunologic function and gut mucosal immunity and its role in prevention of translocation?

What about the role of the liver and secretion of secretory immunoglobulin A in gut mucosal immunity?

Finally you described plasma membrane abnormalities and showed some nice pictures. Are there any differences in the plasma membrane before as well as after translocation has occurred? Are there any peculiarities of the target villi, those that are attacked as opposed to the adjacent ones that are not? What about Peyer's patches? Is the mucosa over Peyer's patches, more susceptible than the remainder of the gut?

CLARENCE DENNIS (Minneapolis, Minnesota): Years ago, when I was working on the appendix, I found that if one removes a normal human appendix and immediately puts it under sterile circumstances on a cannula, it takes culture of the serosa immediately then grows nothing. If, however, you raise the pressure within the lumen of the appendix to less than the diastolic pressure of the individual, and this is human appendix, within 60 seconds you can culture colon bacillus from the serosal surface of the appendix.

It is that easy for bacteria to get through that wall in a piece of intestine that presumably has not yet died from being removed from the organism.

DR. WILLIAM SILEN (Boston, Massachusetts): I rise to point out that current studies by Drs. Paul McNeil and Sus Ito at the Harvard Medical School and Digestive Diseases Center indicate that the slightest amount of trauma, even that which occurs under normal physiologic circumstances (eg, eating), will cause cells in the gastrointestinal tract to disrupt. This work has been published in *Gastroenterology* within the past 6 months.

Lest we get carried away with translocation, the preparation of the Thirty-Vella loop in your experiments can very easily do the same thing.

I have one question for Dr. Alexander. Was there a difference in the incidence of the translocation in the burn *versus* the nonburned groups? Finally, if translocation were so important in multiple-organ failure, then the hundreds of patients who have ulcerative colitis and Crohn's disease should die of it.

DR. CARLOS A. PELLEGRINI (San Francisco, California): Could the authors tell us what were the pressures in the lumen of these bowel loops? I am asking that because when we studied cholangiovenous reflux of particles and bacteria we found that reflux from the lumen of the bile duct to the sinusoids is dependent on the pressure within the bile duct. In other words, whether bacteria reflux or not, and to what extent is a function of luminal pressure.

The second question is: Have they studied any other segments of the gut to see if the process is the same?

DR. ISIDORE COHN, JR. (New Orleans, Louisiana): When we were studying strangulation intestinal obstruction a number of years ago, we realized that bacteria and bacterial products got into the peritoneal fluid before we could detect any break in the intestinal wall either by looking at it or by ordinary light microscopy, and so we enlisted the assistance of the electron microscopist in the department of anatomy.

We did serial studies of loops of bowel before strangulation obstruction, and this is a normal segment of bowel under the scanning microscope. Studies were done at different times after the strangulation obstruction, and the microscopist tells us that this was the first time these pits were described between cells. As we studied things later, we concluded that bacteria and other things could get from the lumen of the bowel into the peritoneal fluid through these pits, which actually represented connections between the lumen and the outside.

This is a serosal surface of a normal bowel.

We did not follow this through in the beautiful way that Dr. Alexander has today, but I think the idea was there.

We made the mistake of calling this "transmigration" instead of "translocation," but this is a slide that was presented at the Southern Surgical Association 18 years ago. I think there is much better follow-up today than we were able to do.

DR. PAUL H. JORDAN, JR. (Houston, Texas): Mr. President, I am confused, particularly by Dr. Silen's discussion.

I would like to go away from this meeting thinking that I had gotten my problems all cleared, but I don't, and my question is: We read all this in the literature how good the gut is and how much better it is to feed the sick patient through the gut than it is through the vein.

Now, is this true or not, and if it isn't true, is this translocation that supposedly is going on with parenteral feeding?

DR. J. WESLEY ALEXANDER (Closing discussion): First I would like to discuss the problem of clinical relevance that was brought up by several individuals. This is certainly an unsettled question at this time, and it will take more laboratory and clinical investigations to prove irrelevance on a very sound scientific basis. However the overwhelming wave of evidence at the present time is that translocation does play a role in some patients, such as a severely injured patient receiving intravenous hyperalimentation. Certainly it does not play a significant role in normal individuals. Whether it plays a role in some patients, such as patients with ulcerative colitis, I think is difficult to say.

We have done further studies in which we have used radioactive labeled *Escherichia coli* and also we have used biotinilated *Candida albicans* in a previous study. It is clear from those studies that the vast majority of organisms that translocate are killed; perhaps less than 1 in 1000 translocated bacteria are actually culturable in the mesenteric lymph nodes. Thus when assessing translocation by culture techniques, only a small fraction is detected, and the amount of translocated but not detected endotoxin may be even more important.

It is also important to note that the pathogens that occur in multiple-system organ failure, *Staphylococcus epidermitis,* E. *coli, Pseudamonas aeruginosa,* and the enterococcus are the organisms that, in the laboratory, are found to translocate more easily. The anaerobes do not translocate, or if they do, they are killed very rapidly and anaerobes seldom cause problems in these particular patients.

Dr. Simmons' studies using the ussing chamber, I think, are particularly interesting. He asked whether *Candida* translocated in normal animals. It does, but to a much lesser degree than after injury. There are a number of things that can influence translocation. One is the number and type of organisms in the gut preventing and inhibiting the translocation process, and another is the concentration of the organisms being studied. If you increase the numbers to very high levels, they will translocate.

Dr. Townsend asked about the model and whether this was an appropriate model to use. I would like to emphasize that we are trying to look at the process rather than the biologic significance, and this is a model in which translocation readily occurs. It is a model using a normal animal that has some atrophy in the gut. We did not measure enzymes or look at other functional properties. It is true that it does not have bile and IGA passing through it, but it is in a situation in which the animal is well nourished, so the question of general malnutrition was removed from this particular model.

I was asked whether Peyers patches were more susceptible to translocation. I would emphasize that translocation occurs throughout the gastrointestinal tract. It has not been well studied quantitatively, but at least in a semiquantitative manner, translocation appears to occur in the ileum to the greatest degree, in the jejunum, to a lesser degree, and in the Peyers patches perhaps a little bit more than in the other ileal segments. It also occurs in the cecum but has not been well studied in the colon, to my knowledge. Thus translocation occurs throughout the gastrointestinal tract, concentrating in the ileal-cecal area.

I was interested in the comments about the passage of bacteria through the appendiceal wall that was brought up by Dr. Dennis and also through the bowel wall, as was brought up by Dr. Cohn, because recently we have done some studies in the laboratory using the burn mouse and E. *coli* that have shown that bacterial do, in fact, pass through the intact bowel wall and can be cultured from the peritoneal cavity.

Dr. Silen asked whether or not organisms would translocate in burn *versus* nonburned animals. They certainly do, but to a much lesser extent.

It is fairly clear that translocation is not important from the clinical standpoint in normal individuals, and it is only those individuals who are subjected to some sort of stress phenomenon, particularly in situations in which there is a decreased blood flow to the intestine, which seems to be a triggering phenomenon for translocation with or without ulcerations.

We did not measure pressures within our loops, but certainly the translocation probe was put in without any pressure, and it was regularly found within 1 hour of the time of injury.

Tumor Necrosis Factor-α Mediates Acid Aspiration-induced Systemic Organ Injury

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Acid aspiration-induced systemic organ injury is mediated by the sequestration of activated neutrophils (PMN). In other settings cytokines have been shown to increase neutrophil–endothelial adhesion, a requisite for injury. This study tests whether the systemic leukosequestration and permeability following localized aspiration is mediated by tumor necrosis factor (TNF)-α–induced synthesis of an adhesion protein. Anesthetized rats underwent tracheostomy and insertion of a fine-bore cannula into the anterior segment of the left lung. This was followed by the instillation of either 0.1 mL 0.1 N HCl (n = 18) or 0.1 mL saline in control rats (n = 18). Localized aspiration induced generalized pulmonary leukosequestration with 95 PMN/10 high-power fields (HPF) in the aspirated lung and 46 PMN/10 HPF in the nonaspirated lung, higher than control values of 7 PMN/10 HPF and 5 PMN/10 HPF in saline- and nonsaline-aspirated sides, respectively ($p < 0.05$). The leukosequestration was associated with permeability edema shown by increased protein concentrations in bronchoalveolar lavage (BAL) of 3900 μg/mL in the aspirated and 2680 μg/mL in the nonaspirated side, higher than saline with 482 μg/mL and 411 μg/mL, respectively ($p < 0.05$). There was generalized pulmonary edema following aspiration measured by increase in wet-to-dry weight ratios (w/d) of 6.6 in the aspirated and 5.1 in the nonaspirated lung, higher than control values of 3.5 and 3.4, respectively ($p < 0.05$). Localized aspiration led to systemic leukosequestration documented by increases in myeloperoxidase activity (units/g tissue) of 2.2 and 1.7 in heart and kidney, higher than control values of 0.3 and 0.4, respectively ($p < 0.05$). This event was associated with edema of these organs with w/d ratios of 4.6 and 4.3, relative to control values of 3.0 and 3.4 ($p < 0.05$). Treatment of animals (n = 18) 20 minutes after aspiration with anti-TNF-α antiserum (rabbit anti-murine) but not normal rabbit serum (n = 18) reduced lung leukosequestration in the aspirated and nonaspirated segments (61 and 32 PMN/10HPF), BAL protein concentration (1490 and 840 μg/mL), and w/d ratio (4.3 and 3.7) (all $p < 0.05$). In the heart and kidney there were reductions in myeloperoxidase activity (0.7 and 0.6) and w/d ratio (3.5 and 3.6) (both $p < 0.05$). Treatment of rabbits (n = 18) with the protein synthesis inhibitor cycloheximide, 0.2 mg/kg/hr was as effective as TNF-α antiserum in modifying aspiration injury. The data indicate that TNF-α mediates acid aspiration-induced local and multisystem organ injury, in part by a mechanism involving an inducible endothelial adhesion protein.

ACID ASPIRATION LEADS to local lung and systemic organ injury, events mediated, at least in part, by neutrophils (PMN). Thus 30 minutes after aspiration PMN have increased oxidative activity shown by flow cytometric assay of peroxide products[1] and after 2 hours have enhanced eicosanoid synthesis.[2] Subsequently these neutrophils are sequestered in the lungs and systemic organs. Inhibition of PMN oxidative activity and sequestration can be accomplished by blocking synthesis of thromboxane (Tx). This will also reduce lung injury.[1,2]

In acid aspiration, lung leukosequestration is thought to represent neutrophil adhesion to microvascular endothelium and not an embolic event with mechanical plugging of neutrophil aggregates. This postulate is based on studies of the respiratory failure that accompanies experimental shock and ischemia in which antibodies against neutrophil-adhesion receptors prevented increased vascular permeability.[3,4] The process of neutrophil–endothelial adhesion occurs not only as a result of PMN stimulation but also involves endothelial activation. This latter event has been shown to be mediated by cytokines. Thus incubation of endothelial cells in culture with tumor necrosis factor (TNF-α) or interleukin-1 (IL-1) induces

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expression of at least two endothelial adhesion molecules, described as endothelial leukocyte adhesion molecule (ELAM) and intercellar adhesion molecule (ICAM).[5,6] Infusion of authentic TNF in rats leads to lung and systemic organ failure associated with leukosequestration.[7] This study tests whether acid aspiration leads to TNF-α–mediated neutrophil sequestration *via* synthesis of an endothelial adhesion protein and tests also the relationship of this event to the local and systemic organ injury.

Methods

Animal Preparation

Ninety-four adult male Sprague-Dawley rats (Charles River Lab, Wilmington, MA) weighing approximately 500 g were anesthetized with intraperitoneal ketamine (35 mg/kg). A jugular venous catheter was inserted for fluid or drug infusion (1 mL/hr) and hourly intravenous anesthetic dosing (ketamine, 8 mg/kg; xylazine 1 mg/kg). A tracheostomy was performed with a 15-gauge tube. Through this tube a fine-bore polyester cannula with an external diameter of 0.61 mm and an internal diameter of 0.28 mm was introduced into the anterior segment of the left lung, which represents approximately one third of the weight of the left lung. Catheter placement was determined by the natural trajectory of the catheter, which invariably entered the anterior segment. All animals were supine for the duration of the experiment.

Preparation of Solutions

Hydrochloric acid. One-tenth milliliter of 33% HCl (Sigma Chemical Company, St. Louis, MO) was mixed with 9 mL of 0.9% NaCl to a final concentration of 0.1 N. When aspirated in a volume of 0.1 mL, the mortality rate within 3 hours was less than 10%. HCl-induced injury is concentration and volume dependent. Thus 0.05 N HCl did not induce systemic organ edema. In concentrations greater than 0.2 N or volumes greater than 0.2 mL of 0.1 N HCl, the mortality rate increased to more than 30%.

Rabbit anti-murine TNF-α antiserum. This antiserum (IP:400, Genzyme Corp., Boston, MA) was derived from New Zealand rabbits immunized with recombinant murine TNF-α. The serum was sterilized using a 0.22-μ filter. It has a neutralizing activity of approximately 10^6 TNF-α units per milliliter and has no cross-reactivity with TNF-β, IL-1, or Γ interferon.

The stock solution of 1 mL was diluted 1:250 with saline and 1 mL was infused intravenously for 5 minutes, 20 minutes after acid aspiration. In preliminary experiments, this concentration of TNF-α antiserum was effective in preventing injury. It neutralized 4000 units of purified native murine TNF-α, an amount greater than that expected in sepsis.[8]

Rabbit serum. Sterile normal rabbit preimmune serum (IP:00 Genzyme Gorp.) was diluted and given in the same volume as IP:400. Endotoxin content of both IP:00 and IP:400 was less than 1 pg/mL in the total volume of serum infused, as assayed with the Limulus amebocyte lysate (Associates of Cape Cod, Falmouth, MA).

Cycloheximide. This agent (Sigma Chemical Co., St. Louis, MO) in powder form was dissolved in saline to a final concentration of 0.5 mg/mL. It was infused in dosage of 0.2 mg/kg/hr, starting 20 minutes after aspiration.

Assays

Myeloperoxidase (MPO). Activity of this neutrophil enzyme was used as a tracer to quantitate PMN sequestration in systemic tissue and it was found to be a more sensitive assay for the detection of entrapped neutrophils than quantitative histology. It was assayed immediately on removal of tissue specimens.[9,10] One gram of tissue blotted dry was homogenized in 10 mL of 0.01 mol/L (molar) potassium phosphate buffer (PPB, pH 7.4) containing 1.0 mmol/L (millimolar) ethylene diamine tetracetic acid (EDTA). Two milliliters of homogenate and 5 mL of 0.01 mol/L PPB containing 1.0 mmol/L EDTA were mixed gently and then centrifuged at 10,000*g* for 20 minutes at 4 C (PR-2 centrifuge, International Equipment Co., Boston, MA). The pellet was rehomogenized in 5 mL of 0.05 mol/L PPB (pH 6.0) containing 0.5% hexadecyltrimethylammonium bromide. This suspension was freeze thawed and sonicated with a Branson cell disrupter (Heat Systems, Ultronics, Plainview, NY) at 65 Watt for 1 minute. A 0.1-mL aliquot was mixed with 0.79 mL of 0.08 mol/L PPB (pH 5.4) and 0.1 mL Of 16 mmol/L tetramethylbenzidine (Sigma) dissolved in N,N-dimethylformamide (Sigma) at 37 C. After 2 minutes, 0.01 mL of 30 mmol/L H_2O_2 was added. After incubating 3 minutes at 37 C, 0.05 mL of catalase solution, 300 μg/mL, was added. The mixture was diluted with 4 mL of 0.2 mol/L sodium acetate (pH 3.0) and then centrifuged at 12,000*g* for 10 minutes at 4 C. The supernatant was read in a spectrophotometer (Spectronic 601, Milton Roy, Rochester, NY). One unit of MPO activity was defined arbitrarily as the amount of enzyme necessary to catalyze an increase in absorbance of 1.0 per minute at 655 nm at 37 C.

White blood cell count. Circulating white cells were quantitated by phase microscopy.

Experimental Protocol

Evans blue dye (0.2 mg) was added to HCl or the saline solution used for aspiration for later documentation of the aspirated lung region. Twenty minutes after HCl aspiration, animals were treated with saline 0.9% (n = 18), anti-TNF-α antiserum (IP:400; n = 18), rabbit serum (IP:00; n = 18), or cycloheximide (n = 18). After saline aspiration animals were treated with intravenous saline 1 mL/kg/hr (n = 18) or cycloheximide 0.2 mg/kg/hr (n = 4). All groups received the same amount of intravenous saline. The intrabronchial cannula was removed after aspiration. Three hours later the animal was killed with an overdose of 200 mg ketamine. A thoracotomy was performed and the right and then left lung bronchus were clamped. Bronchoalveolar lavage of the left lung, including the aspirated segment, and then right lung was performed with 3 mL of saline per side using the tracheostomy tube. This was repeated three times. The combined lavage return of about 8 mL on each side was introduced into tubes containing 0.3 mL of 0.07 mol/L EDTA. This BAL fluid was centrifuged at 1500*g* for 20 minutes (GLC-1 Centrifuge, Sorfall, Newtown, CT), frozen at − 20 C, and subsequently used for protein assay using the spectrophotometric protein dye method.[11] Six rats from each experimental group were used for these protein lavage studies. Another six rats were used to calculate the wet to dry weight (w/d) ratios of the aspirated and nonaspirated lung segments. This ratio was calculated after weighing the dyed segment of freshly harvested lung tissue, heating the segment at 90 C in a gravity convection oven (Precision Scientific Group, Chicago, IL) for 72 hours, and weighing the residuum. A similar method was used to measure the w/d ratio of the heart and kidney. A final six animals from each group were used for lung histology. After these rats were killed, the lungs were perfused with 10% formaldehyde and then inflated with the same material to a pressure of 25 cm H_2O. Following fixation sections from dyed and contralateral segments were stained with hematoxylin and eosin for light microscopic analysis. All microscopic sections were interpreted in a blinded fashion by a pulmonary pathologist (LK). Lung sequestration of PMNs was quantitated by counting alveolar septal wall PMNs in the dyed segment and in the contralateral segment. Only peripheral lung parenchyma was examined. Microscopic fields containing other structures such as airways, large vessels, and pleura were excluded. Leukocyte entrapment was expressed as the mean number of PMN per 10 high-power fields (× 1000).

Results are presented as mean ± SEM in figures. Significance between means was first tested by an analysis of variance and then by a nonpaired Student's t test. Significance was accepted if $p < 0.05$.

Animals in this study were maintained according to the guidelines of the Committee on Animals of the Harvard Medical School and those prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (Department of Health, Education and Welfare, Publication No. 78-23 [National Institute of Health], revised, 1978).

Results

Three hours after localized acid aspiration, there was generalized lung leukosequestration of 95 ± 8 PMN/10 HPF in the aspirated and 46 ± 3 PMN/10 HPF in the nonaspirated side, higher than saline aspiration values of 7 ± 2 PMN/10 HPF and 5 ± 3 PMN/10 HPF, respectively (both $p < 0.05$; Fig. 1). Permeability was increased, as shown by elevated protein concentration in BAL fluid of 3900 ± 280 μg/mL and 2680 ± 210 μg/mL in the aspirated and nonaspirated lungs, higher than 482 ± 62 μg/mL and 411 ± 122 μg/mL in saline-aspirated animals (both $p < 0.05$; Fig. 2). The permeability was accompanied by pulmonary edema as shown by an increase in w/d weight ratio of 6.6 ± 0.4 in the aspirated and 5.1 ± 0.3 in the nonaspirated lung, higher than control values of 3.5 ± 0.3 and 3.4 ± 0.2 (both $p < 0.05$; Fig. 3).

Aspiration led to systemic leukosequestration indicated by increased myeloperoxidase activity of 2.2 ± 0.4 U/g in heart and 1.7 ± 0.4 U/g in kidney, higher than control values of 0.3 ± 0.1 U/g in heart and 0.4 ± 0.1 U/g in kidney (both $p < 0.05$; Fig. 4). There was also an increase in w/d weight ratios of these organs: the heart was 4.6 ± 0.1 and kidney 4.3 ± 0.1, higher than control values of 3.0 ± 0.2 and 3.4 ± 0.1 (both $p < 0.05$; Fig. 5).

Pretreatment of animals with TNF-α antiserum attenuated the aspiration-induced leukosequestration, 61 ± 4 PMN/10 HPF and 32 ± 3 PMN/10 HPF in the aspirated and nonaspirated sides; protein concentration in BAL, 1490 ± 110 μg/mL and 840 ± 100 μg/mL; and w/d weight ratios 4.3 ± 0.2 and 3.7 ± 0.2 (all $p < 0.05$). There was

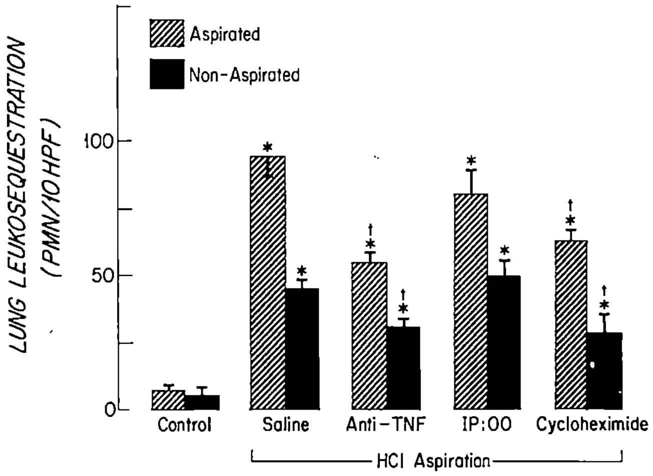

FIG. 1. Localized acid aspiration led to generalized lung leukosequestration. TNF antiserum (but not normal serum) and protein synthesis inhibition attenuated this event. * and † indicate $p < 0.05$ relative to control and saline-aspirated groups, respectively.

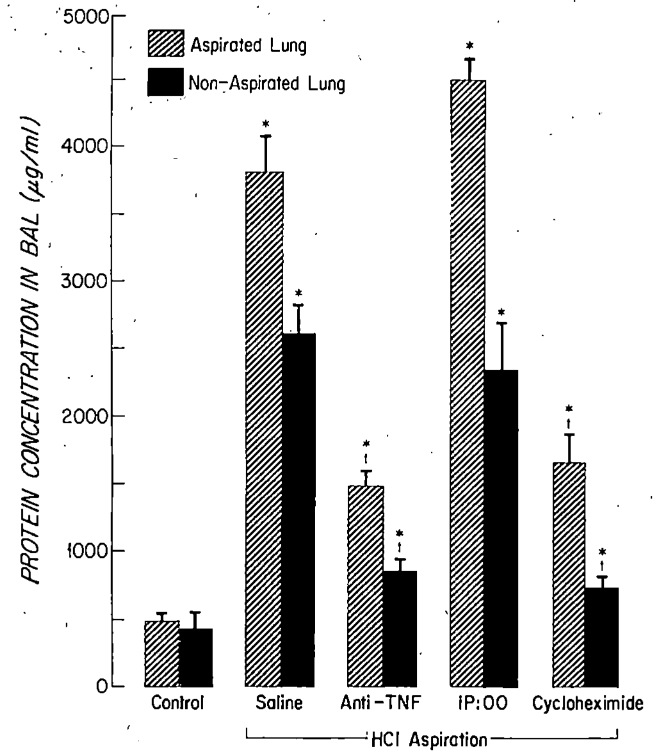

FIG. 2. Localized acid aspiration led to protein leakage in the aspirated and nonaspirated sides. Treatment of animals 20 minutes after aspiration with TNF antiserum or a protein synthesis inhibitor reduced this effect. * and † indicate $p < 0.05$ relative to control and saline-aspirated groups, respectively.

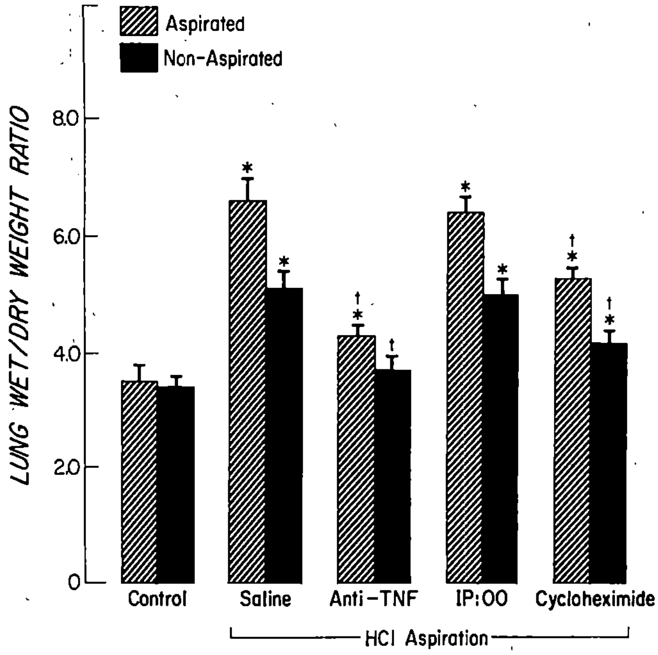

FIG. 3. Localized aspiration led to increase in w/d ratios of both the aspirated and nonaspirated lungs, an event attenuated with TNF antiserum and cycloheximide. * and † indicate $p < 0.05$ relative to control and saline-aspirated groups, respectively.

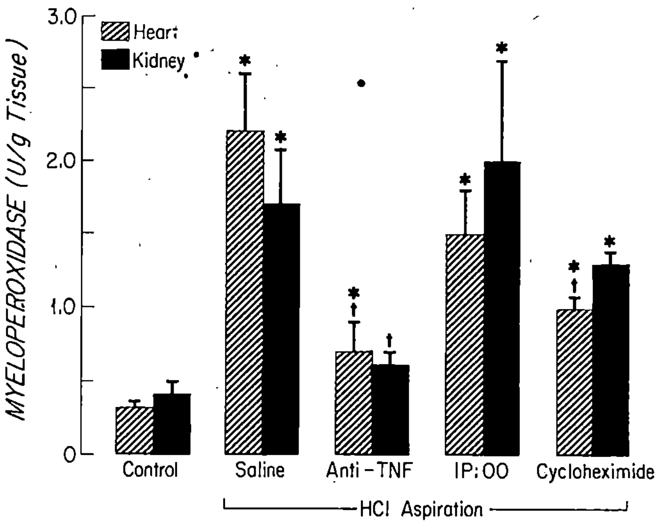

FIG. 4. Three hours after aspiration there was increased myeloperoxidase activity of heart and kidney. TNF antiserum reduced this event. However cycloheximide reduced only heart MPO activity. * and † indicate $p < 0.05$ relative to control and saline-aspirated groups, respectively.

also systemic protection with the anti–TNF-α antiserum, with reduction in MPO activity in heart and kidney to 0.7 ± 0.2 U/g and 0.6 ± 0.1 U/g and w/d weight ratio of these organs to 3.5 ± 0.1 and 3.6 ± 0.2 (all $p < 0.05$).

The TNF-α antiserum in a dilution of 1:500 showed no protection ($n = 4$) because lung leukosequestration was 81 ± 8 PMN/10 HPF and 42 ± 5 PMN/10 HPF, and

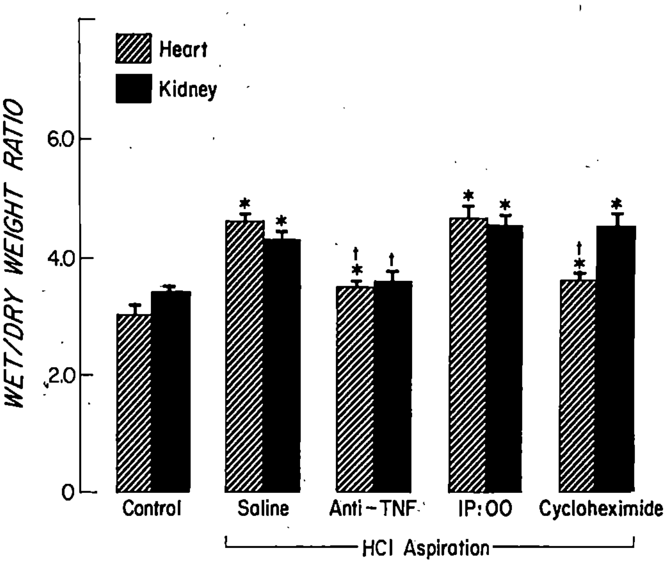

FIG. 5. The increase in MPO activity of heart and kidney after aspiration (Fig. 4) was associated with increases in w/d ratio of these organs. TNF antiserum and cycloheximide reduced MPO activity and the w/d increase of the heart. However cycloheximide did not reduce MPO activity or the w/d increase of the kidney. * and † indicate $p < 0.05$ relative to control and saline-aspirated groups, respectively.

lung w/d weight ratios were 6.0 ± 0.5 and 4.9 ± 0.3. Increased concentration of this agent at a dilution of 1:100 (n = 4) gave no further protection relative to 1:250: lung w/d weight ratios were 4.3 ± 0.4 and 3.7 ± 0.3. The preimmune rabbit serum (IP:00) was without effect (Figs. 1 to 5). Treatment of animals with cycloheximide attenuated aspiration injury: lung leukosequestration was 64 ± 2 PMN/10 HPF and 30 ± 7 PMN/10 HPF in the aspirated and nonaspirated sides; protein concentration was 1760 ± 280 μg/mL and 720 ± 90 μg/mL; and lung w/d weight ratios were 5.3 ± 0.2 and 4.2 ± 0.2 (all $p < 0.05$). Cycloheximide also attenuated the acid-induced heart edema, with w/d of 3.6 ± 0.1 ($p < 0.05$) but not kidney edema, with w/d of 4.5 ± 0.2.

Saline-aspirated animals given the standard cycloheximide infusion of 0.2 mg/kg/hr developed increased PMN sequestration in the lungs with 22 ± 2 PMN/10 HPF ($p < 0.05$ relative to saline infusion) but otherwise showed no difference relative to noncycloheximide-infused saline-aspirated controls with regard to w/d values: lung 3.4 ± 0.1, heart 3.0 ± 0.1, and kidney 3.3 ± 0.1. Infusion of a higher dosage of cycloheximide 0.5 mg/kg/hr in saline-aspirated control animals (n = 6) led to even greater leukosequestration of 50 ± 4 PMN/10 HPF. Again there were no abnormalities in w/d ratios. Saline-aspirated rats given 0.2 mg/kg/hr cycloheximide did not develop increased MPO activity of the heart 0.2 ± 0.1 or kidney 0.8 ± 0.2 U/g relative to saline-infused animals. After HCl administration cycloheximide reduced MPO of the heart to 0.96 ± 0.1 ($p < 0.05$) but not kidney, which was 1.26 ± 0.1 U/g (Fig. 4).

Acid aspiration led to leukopenia of 2650 ± 300 WBC/mm^3 within 1 hour, relative to control values of 10,500 ± 570 WBC/mm^3 ($p < 0.05$). The leukopenia was not affected by TNF-α antiserum, 2460 ± 195 WBC/mm^3 or the preimmune rabbit serum 2695 ± 250 WBC/mm^3

Discussion

The data from this study suggest that TNF mediates acid aspiration-induced local and systemic injury by a mechanism that involves, at least in part, the upregulation of neutrophilendothelial adhesion receptors, a step requiring protein synthesis. These conclusions are supported first by the ability of TNF antiserum to reduce lung and systemic organ leukosequestration and second by the ability of cycloheximide, a protein-synthesis inhibitor, also to attenuate leukosequestration. Third both TNF antiserum and cycloheximide reduced lung and systemic organ permeability and edema.

Tumor necrosis factor may be produced by monocytes and/or pulmonary macrophages, directly stimulated by the aspirated acid. Evidence for TNF production and activity in our setting of aspiration is based on the effectiveness of TNF antiserum. That this cytokine can induce such effects has been documented in other studies in which infusion of recombinant TNF in rabbits and guinea pigs led to pulmonary leukosequestration and edema.[12,13] Similarly a systemic inflammatory response that is manifest by sequestration of neutrophils in lungs, kidneys, and other organs associated with multisystem organ failure occurs in rats after TNF infusion.[7]

In other settings of lung injury and systemic organ failure, TNF has been found to be a mediator. Thus treatment of animals with a monoclonal TNF antibody protected them against neutrophil-dependent systemic organ injury after sepsis or shock.[14,15] Furthermore genetic deficiency in the gene responsible for TNF synthesis inhibited the development of multiorgan failure in an experimental model of the adult respiratory distress syndrome involving gram-negative bacteremia.[16]

Leukosequestration in the lungs and systemic organs is probably based on mechanisms involving neutrophil and endothelial adhesion receptors. Within 30 minutes after acid aspiration, high plasma levels of leukotriene (LT)B$_4$ and thromboxane (Tx)B$_2$ appear (unpublished data). Leukotriene B$_4$ and possibly TxA$_2$ can rapidly, within minutes and without the requirement of protein synthesis, upregulate the neutrophil CD18 adhesion-receptor complex.[17] This could permit neutrophil adherence to basally expressed endothelial adhesion receptors, an event that likely accounts for the early neutropenia.[18] Tumor necrosis factor is an activator of neutrophils, upregulating surface expression of CD 18 and stimulating oxidative activity, the latter event lasting several hours.[19] Tumor necrosis factor also might upregulate CD18 indirectly by stimulating neutrophil synthesis of LTB$_4$ and TxA$_2$.[20] However failure of the TNF antiserum to modify the neutropenia that occurred at 1 hour and that is interpreted as an indication of microvascular sequestration of activated neutrophils argues strongly against TNF involvement in early neutrophil activation.

Treatment of endothelium *in vitro* with TNF induces expression of two varieties of endothelial adhesion receptors, ELAM-1 and ICAM-1, in a process requiring protein synthesis. Thus when a protein-synthesis inhibitor such as cycloheximide is added to the medium, endothelial adhesion receptor upregulation is prevented.[18] Expression of these endothelial adhesion molecules occurs during the course of 2 to 3 hours. This timing is consistent with previous studies showing the delayed occurrence of lung leukosequestration, 2 to 3 hours after aspiration.[1] In this study of acid aspiration, the importance of the endothelial adhesion component in leukosequestration is shown by the effectiveness of TNF antiserum in decreasing neutrophil entrapment. That this endothelial adhesive component requires protein synthesis is confirmed by the cycloheximide data.

Treatment with cycloheximide showed similar reduction in the degree of leukosequestration as the anti-TNF antibody, suggesting similarity of action, that is, inhibition of TNF upregulation of endothelial adhesion receptors in the microvasculature of all organs of the body. The action of this agent, however, is complex. Cycloheximide does not affect expression of the neutrophil CD18 complex.[18] Interpretive problems arise because cytokines are not stored. Cycloheximide could inhibit TNF activity by blocking production of enzymes that are required for its *de novo* synthesis. There is no information to resolve this possibility. Furthermore this agent, in high doses, led paradoxically to lung leukosequestration in control saline-aspirated animals. Even in lower dosage, cycloheximide promoted leukosequestration in controls. This effect may explain its limited ability to reduce MPO activity and prevent the increase in w/d ratio of the kidney, an organ where perhaps the balance of adhesive receptors and adhesive inhibitory factors may favor the latter. Thus cycloheximide could promote renal leukosequestration by synthesis inhibition of an adhesion-inhibitory factor, such as interleukin-8, an event reported *in vitro*.[21] These arguments do not mitigate the conclusion that cycloheximide reduced lung leukosequestration after aspiration.

The inability of the TNF antiserum to fully prevent leukosequestration implies the operation of other mechanisms that lead to PMN–endothelial interaction. Thus other cytokines, such as interleukin-1 and interleukin-6, also may induce ICAM and ELAM. The inability of anti-TNF antiserum to fully prevent PMN adhesion is probably not due to the involvement of these other cytokines because cycloheximide would have largely negated the effect of all such agents as inducers of ICAM-1 and ELAM-1. Second upregulated PMN CD18 adhesion molecules may interact with many basally expressed endothelial adhesion molecules, an event not inhibitable by blocking cytokines or protein synthesis. The importance of this mechanism remains to be tested. Finally other pathways of leukosequestration may be operative, such as those involving platelet-activating factor, LTC_4, or thrombin. These are unlikely, however, because they lead to PMN adhesion in a more rapid fashion than observed following aspiration.[22]

That neutrophils are important mediators of microvascular permeability is again shown in this study. Thus there was increased lung permeability to protein as well as gain in the w/d weight ratio of the lungs, heart, and kidney associated with leukosequestration. Tumor necrosis factor antiserum, but not control serum, attenuated aspiration-induced local and systemic organ leukosequestration, reduced protein leakage in the lung, and reduced lung and systemic organ edema. Similar vascular barrier protection was achieved with cycloheximide and also was associated with reduction in neutrophil sequestration.

A disparity can be seen between the relatively modest 30% to 40% reduction in leukosequestration and the more than 60% reduction in protein concentration in BAL and w/d weights of the lungs, heart, and kidney. These results suggest that, in addition to the action of TNF as an inducer of neutrophil sequestration, it may have other injurious effects. Tumor necrosis factor has been shown to induce increased microvascular permeability without neutrophils. Thus in severely neutropenic sheep an infusion of TNF led to increased lung permeability. Furthermore TNF, in a concentration-dependent manner, increased permeability of an endothelial monolayer to albumin in the absence of PMN.[23]

The data of this study suggest that TNF-α mediates, in part, acid aspiration-induced local and systemic leukosequestration and edema probably by a mechanism involving the expression of endothelial adhesion proteins.

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DISCUSSION

DR. JOHN SIEGEL (Baltimore, Maryland): Dr. Hechtman and his colleagues have presented an exemplary study of the role of TNF in the pathogenesis of acid aspiration pneumonitis. They have noted that one possible mechanism of its action is stimulation of the endothelial cell to produce the ELAM and ICAM adherence proteins. They have showed that some of the effects of acid aspiration can be largely prevented, at least up to 30% with regard to the lung leukosequestration, by the use of an anti-TNF antibody. The anti-TNF antibody also reduced the leakage of protein into the bronchoalveolar lavage fluid in both the HCL aspirated and the nonaspirated lungs and returned the lung and heart wet-to-dry weight values toward control values. All of these effects simulate those produced by cycloheximide.

The work is well designed and, having looked carefully at the methods and the data in this paper, these are certainly statistically significant results.

The important thing, however, is that the TNF effect, which is blocked by the antibody, only represents about one third of the total HCL effect, at least with regard to the lung leukosequestration.

To my way of thinking, some of the more intriguing questions, which perhaps Dr. Hechtman might address, are related to the cause of the residual non-TNF antibody-inhibited leukosequestration and permeability effects following HCL administration, because there were substantial residual effects in both the lung and the heart that are not prevented by either TNF or by the protein synthesis inhibitation, due to cycloheximide.

Perhaps Dr. Hechtman might speculate on a balanced perspective of the role of anti-TNF in the sequence of HCL-induced lung injury and how this relates to his concept of the genesis of ARDS in general.

The studies of the ARDS syndrome in humans, as well as in animals, have shown that there seems to be a longer time period sequence to the evolution of the lung disease, and that the eicosanoids, especially leukotriene B4 and PGE2, rise immediately after injury. These eicosanoid increases are followed by thromboxane and PGF1 increases and all of these responses precede the leukocyte activation and probably also antecede the TNF elevations.

How do Dr. Hechtman and his colleagues view the eicosanoid changes, and the PAF response, which also has been thought to be an inducer of cytokine activation, as interacting with TNF to produce these lung syndromes? Does he think that the lung aspiration response is different from the post-traumatic ischemia responses that he has looked at in earlier work?

Is leukosequestration sufficient to produce ARDS? What we have seen clinically is that patients with severe injuries (ISS scores greater than 20) all have leukosequestration, but only about 30% or 40% of these patients with high ISS score actually develop an ARDS syndrome.

In addition our studies suggest that while circulating TNF levels do increase after severe injury leading to ARDS, they do not rise until after the initial eicosanoid response. Perhaps Dr. Hechtman might give us his thoughts as to how the HCL aspiration model that he has presented to us relates to his own early work using a peripheral ischemia model and to the human observations.

In closing I would like to point out that I think this is a paper of major importance because it does point out a potential modality for therapeutic intervention, at least in modulating the HCL aspiration syndrome. Perhaps it also will provide us with a therapeutic modality that we may use to ameliorate the ARDS syndrome following injury.

DR. HARVEY J. SUGERMAN (Richmond, Virginia): This is a very interesting study that again demonstrates systemic organ injury from the generalized release of inflammatory mediators in a nonseptic state as a result of a single, severe organ injury.

Although the authors' conclusions seem reasonable, it would have been a much tighter study if they had measured an increase in TNF-alpha activity following the installation of acid and if this activity itself was blocked by their TNF-alpha antiserum.

It would also have helped prove their hypothesis if they measured an upregulation of either the leukocyte or endothelial adherence proteins, such as CD-18, and if this upregulation was blocked by either TNF-alpha antiserum or cyclohemamide. A monoclonal antiserum to the CD-18 leukocyte receptor is available and can be used to quantitate CD-18.

It would also be interesting if the CD-18 antiserum, or the TNF antiserum, could prevent the systemic injuries noted. Have the authors measured TNF-alpha activity or the leukocyte or endothelial adherence proteins in more recent studies?

The failure of TNF-alpha antiserum to prevent the systemic leukopenia is inconsistent with the authors' hypothesis. What are your thoughts regarding this discrepancy?

Although the model documented systemic effects of unilateral lung acid instillation, I am not aware of data documenting multisystem organ injury in humans following aspiration injury. Nevertheless systemic injury probably does result from a single, severe organ insult, such as acid aspiration, a crushed extremity, or a severe burn. Studies such as this should help find the path to prevent or reduce damage to other organs in the line of fire!

DR. DAVID HERNDON (Galveston, Texas): I would like to echo Dr. Siegel's comments that this is a major contribution to the literature and not only shows us possible therapeutic ramifications but also a mechanism whereby TNF alpha affects upregulation of adherence proteins.

I have a few technical questions, however. The exact quantity of fluid used to induce the injury was not clear to me. I am especially interested in this because they indicated that there was pathology in the nonaspirated lung, this being a unilateral lung aspiration model. In large animal models in which we produced inhalation injury with cotton smoke, we were unable to show the injury in the contralateral lung, which was insufflated by air.

I was concerned that in these smaller animals some of the aspirate may have gotten into the other lung without occlusive devices to prevent that.

The increase in myeloperoxidase seen in the kidney and heart are indeed most interesting. The lack of linkage of TNF to the protein synthesis effect here is of some concern to me, and I would like a little further discussion in that area.

Do you have data from the lung that would give similar myeloperoxidase levels for comparison? It would also be of interest to know whether blood neutrophil counts in these animals are elevated just before the animals are killed.

You showed an initial neutropenia, but in other studies an elevation shortly after the transient neutropenia has been reported. Could the changes in myeloperoxidase reflect this rather than adherence of the neutrophils?

The only indication that we have of damage is the measurement of tissue waters from the various organs. In the manuscript, histologic examination was performed, and certainly the tissues have been examined when counting for leukocytes. Was there, in fact, evidence of tissue damage? What sort of changes were noted? Was there evidence that the histologic changes were reversed or not when the animals were given the various antiserums?

Infiltration of polymorphonuclear-leukocytes into the tissue and edema formation are noted with ischemia in perfusion injury in your previous studies. What are the cardiovascular changes induced by acid aspiration in this model?

DR. HERBERT B. HECHTMAN (Closing discussion): I thank the discussants for their thoughtful remarks. Let me answer them in sequence. Dr. Siegle's comments related to questions regarding tumor necrosis factor effects and why we inhibited one third of the lung neutrophil sequestration but inhibited perhaps two thirds of the pathologic effects, that is permeability. It is likely that TNF acts directly on the endothelial barrier.

Perhaps one third of the neutrophils were sequestered in the lungs early, before there was any upregulation of endothelial adhesion receptors. That is the neutrophil CD-18 complex does not require protein synthesis for expression. It is upregulated or activated within minutes in a process that is dependent on chemoattractants that are perhaps secreted or in some way gain access into the circulation, particularly leukotriene B_4 and thromboxane. These chemoattractants can rapidly activate CD-18 and lead to neutrophil sequestration by binding to bassely expressed endothelial adhesion receptors, perhaps in all organs of the body. We have been able to reverse this process with an anti–CD-18 monoclonal antibody. The monoclonal antibody that we have used is R15.7. It neutralizes not only the activation of the neutrophil adhesion receptors but also will prevent, in answer to Dr. Sugarman, the leukopenia. This leukopenia is a phenomenon that is totally independent of protein synthesis and independent of cytokine stimulation. The cytokines activate the endothelium. They don't cause upregulation of neutrophil adhesion molecules in these experiments.

Our thesis regarding the sequence of events is that eicosanoid synthesis is induced by aspiration. These eicosanoids, that is leukotriene B_4 and thromboxane A_2 activate CD-18 of circulating neutrophils and produce leukopenia. Furthermore these eicosanoids lead to the synthesis of cytokines that act distantly on endothelial adhesion receptors.

We have tried to measure cytokines, particularly tumor necrosis factor. In only about 20% of our animals are we able to find significant elevations in circulating TNF. Based on this observation, to postulate a TNF effect, we have to look to the current literature that says there is a cell-bound precursor of TNF alpha and that this high molecular weight, cell-bound substance is elaborated into a low molecular weight compound: near the endothelium, in its microenvironment.

The likely cell synthesizing TNF, is the monocyte that is adherent to the bassely expressed endothelial adhesion molecule where it secretes TNF, which causes the endothelium to elaborate new adhesion molecules. We have no other explanation for our failure to measure elevated circulating levels of TNF.

The question of the operation of this sequence of events in ARDS is relevant. In our other studies of ischemia and reperfusion lung injury, we have been very careful to say that a reversible pathologic process has been induced. The fact that neutrophils adhere and produce permeability does not mean we have irreversible lung damage.

The injury in ARDS is something in addition. Following aspiration, we studied our animals for only 3 hours and I would not propose that this end point allows us to predict or understand how we may later get fibrosis and the more chronic inflammatory changes of ARDS that we see in patients. This is an initial foray into the understanding of how a local injury stimulates the inflammatory process that becomes generalized and focused on multiple organs.

Dr. Herndon, we wedged our catheters into the lung. We documented in every experimental animal that we aspirated that the blue die was only in one segment. We used a tenth milliliter of either saline or a tenth milliliter of 0.1 normal hydrochloric acid and there was no spillage. All of our histologic data are of the distal lung. We excluded bronchi and examined only peripheral lung injuries.

The myeloperoxidase assays were done only in the systemic organs, so I do not have comparative data for the lung with regard to myeloperoxidase levels.

Our control animals showed no neutrophil sequestration, but I think you bring up a reasonable point that after acid aspiration there was an increase in circulating leukocytes before the 3-hour period of killing, and this could have influenced, in some part, the number of neutrophils thought sequestered by histologic examination.

Upper GI Bleeding in an Urban Hospital

Etiology, Recurrence, and Prognosis

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Acute upper gastrointestinal bleeding (UGIB) continues to be a common cause of hospital admission and morbidity and mortality. This study reviews 469 patients admitted to a surgical service of an urban hospital. There were 562 total admissions because 53 patients were readmitted 93 times (recurrence rate, 20%). The most common causes of bleeding, all endoscopically diagnosed, included acute gastric mucosal lesion (AGML) (135 patients, 24%), esophageal varices (EV) (121 patients, 22%), gastric ulcer (108 patients, 19%), duodenal ulcer (78 patients, 14%), Mallory-Weiss tear (61 patients, 11%), and esophagitis (15 patients, 3%). Nonoperative therapy was sufficient in 504 cases (89.5%). Endoscopic treatment was used in 144 cases. Operations were performed in 58 cases (10.5%), including 29% of ulcers. Emergency operations to control hemorrhage were required in only 2.5% of all cases. The rate of major surgical complications was 11% and the mortality rate was 5.2%. There were 58 deaths (12.6%), with 36 deaths directly attributable to UGIB. Factors correlating with death include shock at admission (systolic blood pressure less than 80), transfusion requirement of more than five units, and presence of EV (all $p < 0.001$). Most cases of UGIB can be treated without operation, including endoscopic treatment, when diagnostic endoscopy establishes the source. Subsequent operation in selected patients can be done with low morbidity and mortality rates.

ACUTE UPPER GASTROINTESTINAL (UGI) bleeding occurs frequently, prompting hospital admission or complicating another illness.[1] Despite advances in critical care monitoring and support, mortality rates of 10% to 20% continue to be reported.[2,3] While spontaneous cessation of bleeding occurs in as many as 85% of cases,[4,5] early intervention is required in those in whom bleeding does not stop spontaneously. Endoscopic diagnosis and therapy is now an integral part of the management of these patients.[6]

From the Department of Surgery, Wayne State University, Detroit, Michigan

This study was designed to accurately portray the incidence of endoscopically diagnosed lesions responsible for acute UGI bleeding, as well as to examine the clinical outcome and survival in the milieu of treating primarily emergency patients in a modern, urban university hospital. Particular attention was given to patients who developed bleeding while hospitalized and to those who were admitted for recurrent UGI bleeding.

Methods

This study was performed at Detroit Receiving Hospital, a Wayne State University-affiliated hospital serving a large inner-city population, and focuses on only a subpopulation of a much larger experience of this department.[6] We examined retrospectively the hospital records and endoscopy reports of 469 patients admitted with UGI bleeding during a 4-year period from January 1984 to December 1987. The list of study patients was drawn from endoscopy records. After chart review, the data was processed and analyzed by computer using SPSS/PC$^+$ Version 2.0. Categorical data was analyzed using chi square and Fisher's exact tests, while Student's t test was used to analyze continuous data. Statistical significance was accepted at $p < 0.05$.

As a matter of policy, nearly all patients admitted through the emergency room with the diagnosis of UGI bleeding were admitted to the surgical service. All patients underwent standard resuscitation with crystalloid and blood and were admitted to the intensive care unit as necessary. Endoscopy was performed under the direction of the surgical staff, usually within 24 hours of admission. More than 95% of diagnostic endoscopy and all of the

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therapeutic endoscopy interventions were supervised by a single surgeon. Gastric lavage with room temperature saline was performed through a Salem-Sump or large-bore lavacuator tube before endoscopic examination, which was performed using a standard forward viewing flexible fiberoptic endoscope. When more than one lesion was found, the actual cause of bleeding was defined by the presence of active bleeding or stigmata of recent hemorrhage.[7,8]

Results

Patient Profile

Of the 562 consecutive admissions (469 patients), 53 patients were admitted on multiple occasions. Thirty-two patients were admitted twice, 11 patients were admitted 3 times, 5 patients were admitted 4 times, 4 patients were admitted 5 times, and 1 patient was admitted 9 times. Three hundred thirty-five patients (71.4%) were male and 134 (28.6%) were female. The mean age was 48.6 years (range, 15 to 88 years) and 29% (135 of 469 patients) were more than 60 years old. A history of chronic, moderate, or heavy alcohol consumption was given in 397 of all admissions (71%) and recent heavy alcohol consumption occurred in 288 (51%). Aspirin or nonsteroidal anti-inflammatory agents had been used recently in 103 of the 562 admissions (18%).

Patients presented to the emergency room in 88% of cases (505 of 562) with signs and symptoms of recent UGI bleeding. Fifty-seven patients (12%) developed UGI bleeding during hospitalization for other problems and were referred for evaluation. Presenting symptoms included one or more of the following: hematemesis in 325 (58%), melena in 253 (45%), nasogastric aspirate containing blood or clot in 104 (19%), syncope in 68 (12%), and hematochezia in 56 (10%).

Cause of Bleeding

The primary lesion responsible for bleeding was established by endoscopy in all but two cases (0.02%; Table 1).

TABLE 1. *Cause of Bleeding*

Cause	Initial Admission (%)	Readmissions (%)	Total (%)
Acute gastric mucosal lesions	118 (25)	17 (18)	135 (24)
Gastric ulcer	97 (21)	11 (12)	108 (19)
Esophageal varices	85 (18)	36 (38)	121 (22)
Duodenal ulcer	69 (15)	9 (10)	78 (14)
Mallory-Weiss	52 (11)	9 (10)	61 (11)
Esophagitis	14 (3)	1 (1)	15 (3)
Other	34 (7)	10 (11)	44 (8)
Total	469	93	562

TABLE 2. *Causes of Bleeding: In-hospital (n = 57)*

Primary Diagnosis	n	%
Acute gastric mucosal lesions	15	26
Gastric ulcer	15	26
Duodenal ulcer	13	23
Esophageal varices	4	7
Mallory-Weiss tear	2	4
Esophagitis	2	4
Other	6	10
Total	57	100

The other causes of bleeding in initial admissions included gastric tumor (n = 10), marginal ulcer (n = 9), vascular ectasia (n = 5), duodenitis (n = 4), and gastric varices (n = 4). Two or more endoscopic findings were present in 320 admissions (57%). The endoscopic diagnosis for patients who had a single admission or the first admission for those with multiple subsequent bleeding episodes is shown in the first column on Table 1.

In-hospital Bleeding

The endoscopic diagnoses for the subgroup of 57 patients who developed UGI bleeding while hospitalized for other problems are shown in Table 2. The most common primary problems included cervical spinal cord injury (n = 7), head injury (n = 4), recent major operation (n = 9), wound sepsis (n = 5), pneumonia (n = 7), cirrhosis (n = 4), and sepsis (n = 7).

Recurrent Admission for Bleeding

During the 4-year study period, 416 patients had single admissions, but 53 patients were readmitted a total of 93 times. The endoscopic diagnoses for the second and subsequent admissions for these patients are shown in the second column on Table 1. Many (38%) were readmitted with the same primary lesion noted on their previous admission, and 83% of those with multiple lesions presented on subsequent admissions with the same combination.

Blood Transfusion Requirements

Table 3 shows the amount of blood transfused for each of the major causes of bleeding. The amounts of blood are those given during the entire hospitalization for patients admitted with UGI bleeding or the amount given during an episode of bleeding for those who bled during the course of another illness.

Nonoperative Treatment

Bleeding was managed without operation in 504 of the 562 admissions (89.6%). Initial therapy consisted of restoration of fluid and blood volume and normalization of vital signs with crystalloid and blood administration. La-

TABLE 3. *Diagnosis and Transfusion*

Diagnosis	Units 0–1 (%)	Units 2–5 (%)	Units More than 6 (%)	Total
Acute gastric mucosal lesion	62 (46)	54 (40)	19 (14)	135
Esophageal varices	4 (3)	54 (45)	63 (52)	121
Gastric ulcer	21 (19)	44 (41)	43 (40)	108
Duodenal ulcer	18 (23)	38 (49)	22 (26)	78
Mallory–Weiss	27 (44)	24 (39)	10 (16)	61

vage with room temperature saline through a large-bore nasogastric tube was used routinely. Intravenous vasopressin (0.2 to 0.4 units/minute) was used in 35 cases of esophageal varices, and a Sengstaken-Blakemore tube was used on 25 occasions. Sclerotherapy was performed in 99 cases (82%) of varices. Endoscopic treatment of nonvariceal lesions included injection therapy in 37 cases and thermocautery in eight cases. The main indications for endoscopic treatment of nonvariceal lesions were gastric ulcer (n = 21), duodenal ulcer (n = 9), Mallory–Weiss (n = 5), and acute gastric mucosal lesion (AGML) (n = 4). Of the 45 patients who underwent endoscopic treatment for nonvariceal lesions, 9 (19%) required subsequent surgery, 2 on an emergency basis for the control of hemorrhage, and 7 on an elective basis for definitive treatment of ulcer disease.

Operative Management

Fifty-eight patients underwent surgery. The endoscopic causes of bleeding in these patients were gastric ulcer (n = 29), duodenal ulcer (n = 24), marginal ulcer (n = 1), esophageal varices (n = 3), and gastric carcinoma (n = 1). Emergency operations to control bleeding were required in 14 cases (2.5% of 562 admissions) and 44 cases (7.8%) had semielective procedures performed because of clinical factors such as age, magnitude of blood loss, and previous ulcer history. Twenty-seven per cent of gastric (29 of 108) and 31% of duodenal ulcers (24 of 78) were treated with operated. Fifty-four operations were done for bleeding ulcers, including one marginal ulcer. Vagotomy and pyloroplasty, with or without suture ligation of the bleeding point, was done in 13 cases and partial gastrectomy, with or without vagotomy, was done in 41 cases. Three portocaval shunts for bleeding varices and one total gastrectomy for carcinoma were done. Major complications occurred in six patients (11%). These complications included cardiac arrest (n = 1), pneumonia (n = 1), subphrenic abscess (n = 1), dehiscence (n = 3), bowel obstruction (n = 1), and congestive heart failure (n = 1). Six other patients (11%) had minor complications, including dumping (n = 1), wound or other minor infections (n = 3), and atelectasis (n = 2). There were three operative deaths (5.2%), one after a portocaval shunt and two in the ulcer group (3.7%), both of whom developed bleeding while hospitalized for unrelated problems.

Mortality Rate

The overall mortality rate was 12.6% (59 of 469 patients) or 10.5% of 562 admissions. Table 4 shows the mortality rates of 469 patients by diagnosis. The overall mortality rate in nonvariceal bleeding was 8.6% (33 of 384). In 36 of the total number of cases, death was primarily caused by UGI bleeding, and the ultimate mechanism of these deaths are detailed in Table 5. In the other 23 cases, deaths were caused by underlying disease, including multiple-system organ failure, liver failure, pneumonia, sepsis, CVA, aspiration, and cancer. Of 57 patients who developed in-hospital UGI bleeding, 13 died, including 3 deaths directly attributable to UGI bleeding (5.3% mortality), and 10 from unrelated disease.

Clinical factors that were significant predictors of death are shown in Table 6 and include shock, a more than 5-unit transfusion requirement, and a diagnosis of esophageal varices. Age of more than 60 years was not found to be a significant predictor of mortality (p = 0.1434).

Discussion

Cause of Bleeding

The present series reports a relatively high incidence of esophageal varices, AGML, Mallory–Weiss syndrome, and gastric ulcer as causes of UGI bleeding requiring hospital admission.[9–12] This is probably a reflection of our inner-city population and contrasts with community hospital or multicenter series, in which peptic ulcer disease is the more frequent cause of bleeding,[13–15] although others also have noted a decrease in proportion of duodenal ulcer.[16] Comparison of our data with other series is shown in Table 7.

Few studies examine the incidence of readmissions for UGI bleeding. In a multicenter series, de Dombal et al.[15] report a 50% rate of further bleeding in cases of carcinoma or varices, and further bleeding in 29%, 24%, and 15%

TABLE 4. *Mortality*

Cause of Bleeding	Total Mortality N	Total Mortality %	Mortality Due to UGI Bleeding N	Mortality Due to UGI Bleeding %
Esophageal varices	26	31	25	29
Acute gastric mucosal lesion	12	10	3	3
Gastric ulcer	8	8	4	4
Mallory–Weiss tears	7	13	5	10
Duodenal ulcer	3	4	1	1
Esophagitis	0	0	0	0
Other	3	9	0	0

TABLE 5. *Cause of Death Due to Bleeding*

Exsanguination	13
Liver failure	10
Multiple-organ system failure	7
Respiratory failure	4
Aspiration	2
Total	36

for gastric ulcers, duodenal ulcers, and gastric erosions, respectively. While we found a 20% incidence of rebleeding, without a 'captive' population we cannot discern the true recurrence rates. Esophageal varices were responsible for most recurrences (38%), whereas peptic ulcer disease (both gastric and duodenal) accounted for 28%.

In-hospital Bleeding

We analyzed cases of in-hospital bleeding separately, because the patient population is somewhat different, and found that in these patients UGI bleeding indeed may be a component of sepsis and multiple-organ failure.[3,17] We found that an incidence of gastric and duodenal ulcer is higher than reported by some others, while the incidence of AGML,[3] which has been found as high as 75% in other series,[17] was lower. Incorrectly ascribing UGI bleeding to stress gastritis in hospitalized patients without endoscopic examination may overlook a significant number of ulcers.[18] Endoscopy was performed on these patients only when substantial bleeding occurred, which possibly explains the lower incidence of AGML.

The present series found that close to one half of the patients who bled while hospitalized did so from peptic ulcer disease and about a quarter bled from stress gastritis. Although others[19] have suggested that evaluation of bleeding in hospitalized patients may be deferred, prompt evaluation may be warranted[18] in cases of significant bleeding, as suggested by our data.

Blood Transfusion

Blood transfusion is a mainstay of therapy and also an index of severity. The present series is consistent with others' findings that the number of transfusions correlates with mortality.[2,15,20]

TABLE 6. *Predictors of Mortality*

	Mortality		
Indication	With	Without	Significance
Shock on admission SBP less than 80	28.4% (29/102)	6.5% (30/460)	p < .001
Transfusion more than 5 units PRBC	20.2% (39/193)	5.4% (20/369)	p < .001
Esophageal varices	21.5% (26/121)	7.5% (33/441)	p < .001

TABLE 7. *Frequency (%) of Various Causes of UGI Hemorrhage in Published Series*

Series	Varices	Mallory–Weiss tear	Peptic Ulcer	Acute Gastric Mucosal Lesions
Dagradi (n = 500)[14]	16	3	11	34
ASGE (n = 2097)[12]	15	8	45	30
Larson (n = 115)[3]	11	5	29	41
de Dombal (n = 4.010)[15]	13	2	36	7
This series (n = 562)	22	11	33	24

Only 26% of patients required no transfusion, while other series report that 20% to 36% did not require it. A requirement of more than five units of transfused blood occurred in 31% of cases, which compares to reports of 26% to 34% requiring more than five[3] or six units.[20,21] Varices and gastric and duodenal ulcers are responsible for most of these cases of massive bleeding. We have found also that clinical shock is a significant predictor of mortality, as reported by others.[22,23]

Management

There is still controversy about the value of endoscopy in increasing survival.[1,21,24,25] However the role of endoscopy in guiding therapy, especially by nonoperative means, is probably more important,[4,14] but this is also controversial.[26] Endoscopic therapy was commonly used in this series. This may be responsible for the greater in-hospital survival rate in cases of esophageal varices.[27] Endoscopic control of nonvariceal bleeding,[28,29] even if on a temporary basis, may explain the few cases that required emergency laparotomy for control of bleeding.

Operative Therapy

Surgery was required in 12.4% of patients (58 of 469) and 10.3% of admissions (58/562), but in only 2.5% of admissions was it required as an emergency measure to control hemorrhage. Other series report operative rates of 11.9% to 40%,[3,16,20,30,31] with most surgery done on an emergency basis.[20,32] Our frequency of operations for gastric and duodenal ulcers (27% and 31%) are comparable to other rates,[30] although fewer were required to control bleeding (6% and 10%, respectively). One possible explanation is that endoscopic injection or thermocoagulation[33] afforded temporary control of bleeding and allowed surgery to be delayed until after stabilization of the patient. This may explain our low mortality rate in these cases (two deaths, 3.7%) because emergency operations are associated with a higher mortality rate.[32] Also the overall lower age of this population may be responsible for the lower death rate when compared to studies with older patients.[31] The lower overall rate of surgery in this series is explained in the lack of operations performed for varices,[11] gastritis,[16] and other lesions, and the lower incidence of carcinoma in this population. Early endoscopy may have allowed selection of those patients who would benefit from early operation,[24,34–36] such as peptic ulcer with exposed blood vessel,[7,8] and those in whom nonoperative management would be more prudent, such as AGML, varices, and Mallory–Weiss tears.

Mortality

In this series, we have divided deaths into those that are directly or indirectly attributable to GI bleeding and those that, in our judgment, are secondary to unrelated causes. Table 8 compares mortality figures of recent series for common diagnoses. The mortality rate in this study compares with most other series.

When repeated admissions for varices are considered, the expected mortality rate per admission is 21%, which is similar to other studies considering total admissions. Mallory–Weiss tears in our experience were associated with a higher incidence of death; however all but one of these patients had cirrhosis and coexisting (but nonbleeding) varices.

Unexpectantly the number of deaths did not correlate with age, as reported by others.[3,23] This may be due to the large number of young patients with variceal bleeding who comprise most of the deaths. In series with an elderly patient population, most deaths have been attributed to concomitant medical disease, with ulcers comprising most deaths.[31]

TABLE 8. *Comparison of Mortality in Recent Series (%)*

Series	Esoph. Varices	Duod. Ulcer	Gast. Ulcer	Mallory–Weiss tear	Acute Gastric Mucosal Lesions
Silverstein[20] (1981)	30	7	8	4	10
Larson[3] (1986)	36	8	16	17	27
de Dombal[15] (1988)	31	4	6	2	7
Katschinski[31] (1989)	17	9	12	2	5
This study: initial admission	31	4	8	13	10
Total admission	21	4	7	11	9

Conclusion

In an urban hospital, AGML, gastric ulcer, esophageal varices, and Mallory–Weiss tears are more common than in a community population in which the incidence of duodenal ulcer is greater. There is a high recurrence rate, especially with esophageal varices. Early endoscopy is important in selecting those 89% of patients who can be treated without operation. When surgery is required, it can be done with a low incidence of death. Significant predictors of death include the presence of shock on admission, transfusion requirement greater than five units, and diagnosis of esophageal varices.

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DISCUSSION

DR. KEITH KELLY (Rochester, Minnesota): It was most interesting to note the distribution of cases in this inner city series, a distribution different than we would see at Mayo. We don't have as large a percentage of varices or stress ulcers among our series as does Dr. Sugawa.

There are a couple of other things that struck me about the series and especially about the methods of management, and I would like to concentrate more on the management than on the epidemiology. I notice in the ulcer group that there were 166 patients. Of these, 11 died, but only five died of bleeding. That is a 3% rate of death from bleeding. Thirty per cent of the patients were operated on, which is about the usual percentage, but among these only two died, yielding only a 4% incidence of death after surgery. These results are superb. They are as good as any reported in the literature. Is this because early endoscopy was done by surgeons who controlled most of the tough cases endoscopically?

In contrast to the bleeding ulcer group, the results in the bleeding varices patients were not as good. Here 85 patients were present, and among these 26 died, which is almost one third. Most of the patients who died, died from bleeding. These patients were also endoscoped, and they also had endoscopic therapy, but apparently endoscopic therapy wasn't so good. More recurrent bleeding occurred, and more deaths from that. What I didn't find in the paper was why only a few of these patients were operated on. What about shunt therapy? What about operative control of the bleeders?

I presume that what we are seeing in the varices group is a series of acutely ill patients in an inner city hospital with severe problems of liver failure and bleeding. Nonetheless, I wonder if some of these patients might not have been saved by operation.

DR. PAUL JORDAN (Houston, Texas): I can probably only reiterate much of what Keith Kelly has just commented on. This is an old problem that has been with us and it is going to continue to be with us, and I suppose that under some circumstances it is almost as dramatic as some of the things we have heard here today, such as transplanting a kidney in a baby younger than 1 year old. But sometimes we have a problem with this condition, and I think that the authors are to be commended for the mortality rate they have achieved.

Just to pick one condition, for example, duodenal and gastric ulcer, their mortality rate for surgery was 3.7% and when you consider that 25 or 30 years 30% was an acceptable figure, this is a remarkably good result and one can only speculate that perhaps it is because of the fact that the surgeons have complete control of these patients from the time they come to the emergency room through the diagnostic procedures and the endoscoping therapeutic procedures, as well as being able to make the decision as to when and how to operate on them.

Endoscopy has not only affected this condition in terms of diagnosis but also in therapy.

One of my questions to the authors has been why haven't more cases been successfully treated by sclerosis, and does this mean that it is a failure of the procedure? But in the literature it says that endoscopy has not improved the survival rates of patients with upper GI bleeding, and when you consider the fact that 85%, or I think it was 89%, in this study all upper GI bleeding stopped spontaneously, it is very hard to show that endoscopy changes the survival rate in this condition.

However, for the surgeon, it has been a great source of satisfaction to have some idea of what the diagnosis is when they operate, and another point related to endoscopy is that when patients bleed and when they rebleed in the hospital, and then they stop, you never know when they are going to rebleed again. So I think that every patient who bleeds should be endoscoped as soon as he or she is stabilized if the endoscopy is not already done to try to produce therapy.

There were 196 patients with duodenal and gastric ulcers in this series. Fifty-four of them were operated on, and I think that 20% of the duodenal ulcers patients came back with rebleeding. What were the indications for operation in this series that more of them weren't operated on originally because they had control of the patient?

My thought has always been that in patients who rebleed, the more times they rebleed the higher the mortality rate will be, and so I would have thought that maybe more of the duodenal and gastric ulcers might have been operated on.

DR. BARRY LEVINE (San Antonio, Texas): Their presentation is relevant because it shows us the cold reality of how we fare in treating upper gastrointestinal hemorrhage in an inner city population whose diseases are mostly alcohol related. They have also demonstrated, by using a prescribed algorithm for control of acute hemorrhage and defining subgroups with surgically amenable lesions, that patients can undergo operative therapy electively with a decreased mortality rate.

Obliquely, what I think the group has tried to tell us is that they attempted to define the role of endoscopy in assessing and treating these patients and, perhaps, that use of this modality has allowed them to achieve these better morality rates. However, before they can make such a claim (although I agree with them), they must better define for us what they mean by emergency endoscopy. In their manuscript it states that endoscopy was carried out within 24 hours of admission on all patients. Does this mean that some of these patients were not bleeding by the time they were endoscoped? In fact, had bleeding stopped by itself without directed diagnosis or treatment? If some of these patients had bled from superficial gastric mucosal lesions, and these patients had stopped bleeding by 24 hours, your delayed endoscopy would have only viewed them when they were well on their way to healing.

This report has emphasized that endoscopic findings can direct therapy in many of these patients. Such a finding belies past reports claiming that emergent endoscopy does not change the outcome in upper gastrointestinal hemorrhage. It is true that endoscopy will not change the outcome in such a group if no therapy is instituted based on that endoscopy. However, in this study, therapy was carried out based on what the endoscopist found and, therefore, did make a difference.

Another question that I have concerns the significant number of patients in this group who were noted to have Mallory-Weiss tears in addition to varices and portal hypertension. I know that in our own institution we have some degree of difficulty, when those two findings appear together in a single patient, in assessing the true etiology for the acute bleeding. Generally we agree that such patients are bleeding from esophageal varices and not the Mallory-Weiss tears. The other two discussants have mentioned it, but I will also reiterate that the significant mortality rate that was seen in this series was directly related to bleeding from either esophageal varices or Mallory-Weiss lesions in patients who also had esophageal varices, *i.e.,* the portal hypertension patients. Such patients also accounted for the large number of readmissions for bleeding. Yet only three operative portasystemic shunts were done. Now that I have reviewed this data, I would ask the authors if they plan to change any of their strategies in dealing with these patients.

DR. KENNETH SWAN (Newark, New Jersey): Dr. Zeppa, you introduced me to portal hypertension surgery a number of years ago, and I would like to make a strong plea for its continued use.

The authors indicated a 31% mortality rate for nonoperative treatment of varices, which is what we would expect if the patients were admitted to a medical service, but they were admitted to a surgical service where the surgeon has control. I echo similar questions that others have already raised.

Our own experience with a similar patient population, in terms of Child's classification, consists of almost 100 consecutive shunts, but over a much longer period of time. Our operative mortality rate is 13% for emergency surgery, and 4% for elective surgery. I think these are appropriate figures.

Why didn't the surgeons operate earlier? Certainly after they had controlled bleeding on the first admission they should have operated urgently or electively and not allowed emergency readmission for control of a subsequent hemorrhage. The data, in my opinion, make a strong point for aggressive surgical management of bleeding esophageal varices.

DR. WALLACE RITCHIE (Philadelphia, Pennsylvania): First, you noted high mortality rates with things that we would all have expected, such as bleeding esophageal varices and the magnitude of the bleed, as indicated by the necessity to transfuse more than five units of blood. You also noted a nonassociation with age, which is a little surprising. I wondered, however, if the mortality rate was a function of whether the bleeding developed in the hospital as opposed to out of hospital.

My second question is a little off the beaten path. As we know, the manifestations of acute upper gastrointestinal disease may be a little different in the inner city compared to suburbs. Recently there has been a spate of anecdotal reports about acute perforations of duodenal ulcers in heavy crack users. The use of crack isn't limited to the inner city, but it seems to be a bit more pervasive there, and I wondered if you found any association between your bleeding problems and the use of crack. Probably not, but it would be interesting to speculate about.

DR. J. P. KIM (Seoul, Korea): Dr. Sugawa, I enjoyed your paper very much, and I would like to make a short comment on the cause of the upper GI bleeding.

We analyzed upper GI bleeding cases for 20 years at Seoul National University Hospital and found that gastric cancer bleeding was the third common cause of bleeding, following gastroduodenal ulcer and variceal bleeding.

Maybe this is the geographical difference of the disease pattern, but whenever you see the patients from this area, the Far Eastern countries, including Korea, Japan, and China, I think you must consider that stomach cancer bleeding as a possible cause of upper GI bleeding. And endoscopic biopsy is highly recommended in the patient with gastric ulcer bleeding to diagnose early gastric cancer for cure of the patient.

DR. EDWARD F. PARKER (Charleston, South Carolina): I rise to ask a question about terminology. Because the esophagus is not a part of the gastrointestinal tract, it is part of the alimentary tract, should we change the title to alimentary bleeding in an urban hospital?

DR. C. SUGAWA (Closing discussion): Dr. Kelly, I think modern endoscopic diagnosis helps in the management, and is helping to reduce morbidity and mortality rates. If, on endoscopy, an ulcer is seen to be the cause of bleeding and will obviously require surgical control, the patient can be quickly dispatched to the operating room. However, bleeding from many lesions can be controlled by endoscopic hemostatic techniques. If surgery is indicated for these patients on the basis of other factors, such as age, ulcer history, or magnitude of blood loss, it can be done semi-electively, with the bleeding controlled and after the patient is well stabilized.

There were several questions regarding surgical treatment of variceal bleeders. Many of these patients were very sick, very yellow, had massive ascites, and presented a great risk for shunting. Bleeding in most of these patients can be controlled with endoscopic sclerotherapy, repeatedly if necessary. However their liver disease progresses to end-stage, and at that point they are not candidates for any procedure at all.

Dr. Jordan and Dr. Levine, I think endoscopic control of active bleeding allowed many operations to be done on an elective basis, or avoided in a few very sick patients, and this improved our survival rate. The decision to operate was based on previous history, age, risk of noncompliance with medical regimen, and the magnitude of blood loss, in addition to the severity of the lesion. When a patient was thought to be a surgical candidate, based on these factors, surgery could be promptly done. This, I think, improved our survival rate.

Another reason for the lower mortality rate for ulcers is that being an emergency hospital, most patients are admitted with an upper GI bleed, while we have fewer in-hospital bleeders than others. I think much higher mortality rates would be seen in a university or tertiary referral center population because of the higher number of in-hospital bleeders with concomitant disease.

Dr. Swan, regarding shunt surgery in the variceal bleeders, in our experience results with emergency shunting have been very poor. These patients have severe cirrhosis and continue to drink even after sclerotherapy or surgery, and then return with further bleeding. We believe that in the short term, sclerotherapy gives better results and fewer complications, whereas in the long term, the results are equivalently dismal.

Dr. Ritchie, less than 10%, 57 patients, were in-hospital bleeders who were primarily hospitalized for head or cervical injury, major surgery, or other medical problems. The number of deaths due to bleeding in this group was 5.3%, although their overall mortality rate was 23%.

Dr. Kim, we do not see much bleeding as a result of tumors. I think we had perhaps 10 or 11 patients with tumors, including benign polyps, so it is different over here and in the Far East.

Surgical Therapy in Barrett's Esophagus

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Seventy-six patients with Barrett's esophagus were cared for during a 10-year period. Fifty-six patients (74%) presented with complications of the disease. There were 20 strictures, 7 giant ulcers, 11 cases of dysplasia, and 29 patients with carcinoma. In patients with benign disease, 93% had mechanically defective sphincters and 83% had peristaltic failure of the lower esophageal body. Esophageal pH monitoring showed excessive esophageal exposure to pH less than 4 in 93% and excessive exposure to pH more than 7 in 34% of the patients tested. Ninety-three per cent of patients with excessive alkaline exposure had complications, compared to only 44% with normal alkaline exposure ($p < 0.01$). Gastric pH monitoring, serum gastrin levels, and gastric acid analysis supported a duodenal source for the alkaline exposure. Antireflux surgery was performed using Nissen fundoplication in 30, Belsey partial fundoplication in 3, and Collis-Belsey gastroplasty in 2. Six required resection with colon interposition. Good symptomatic control was achieved in 77% after antireflux surgery. Four patients had symptoms and signs of duodenogastric reflux; three required a bile diversion procedure. Fifteen patients had an *en bloc* curative resection with colon interposition. One patient with high-grade dysplasia on biopsy was found to have intramucosal carcinoma after simple esophagectomy. Five tumors were intramucosal, seven were intramural, and four were transmural. Lymph node involvement occurred only in the latter two. Actuarial survival 5 years after curative resection was 53%. Median survival time for patients after palliative resection or no resection was 12 months. Study of *en bloc* specimens indicated that extent of resection should be adapted to extent of disease: esophagectomy for intramucosal disease, *en bloc* esophagectomy with splenic preservation for intramural and transmural disease. Serum CEA was useful in detecting recurrent disease after surgery when the primary tumor stained positively for CEA.

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COLUMNAR-LINED LOWER ESOPHAGUS, known as Barrett's esophagus,[1] may be complicated by stricture, giant ulceration, hemorrhage, perforation, or malignant degeneration.[2,3] Barrett's esophagus is usually associated with gastroesophageal reflux disease, but the reasons why only a portion of patients with reflux develop Barrett's and only some of these are prone to complications are not known.

Gastric juice generally is regarded as the damaging agent in gastroesophageal reflux disease. Medical therapy is aimed at suppressing its acid component, allowing other components such as duodenal secretions, pancreatic secretions, and bile to continue further tissue destruction. This may explain why medical therapy, as opposed to surgical therapy, which constructs an antireflux barrier, fails to provide complete symptomatic relief in most patients,[4] and allows upward progression of the columnar mucosa.[5] While there is strong evidence for sequential progression from low-grade dysplasia to high-grade dysplasia to invasive carcinoma, there is no consensus on the frequency and tempo of progression and whether progression is influenced by medical or surgical therapy.[6–8] Controversy exists over the appropriateness of surveillance because an improved survival by resection of early cancers arising in Barrett's esophagus has not been well documented.

The aim of this study was to examine the pathophysiology of Barrett's esophagus and the role of surgery in the treatment of the disease and its benign or malignant complications.

Patients and Methods

Patients

Seventy-six patients with Barrett's esophagus were diagnosed during a 10-year period by the endoscopic ob-

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servation of a segment of lower esophagus, at least 3 cm in length, lined by columnar epithelium in continuity with the gastric mucosa, and confirmed by histology. The columnarization extended a median of 6.2 cm over the lower esophagus, with a range of 3 to 18 cm. Twenty patients (26%) presented without complications; 27 (36%) with complications of stricture, ulcer, or dysplasia; and 29 (38%) with invasive malignancy. At endoscopy the strictures were fully dilated to relieve any obstruction before performing physiologic tests.

Table 1 describes the age and sex distribution of the patients with Barrett's esophagus according to the presence and type of complication. Patients with complications were 10 years older than those without complications. Benign complications were more frequent in female (15 of 21 patients or 71%) compared to male patients (12 of 26 patients or 46%). Multiple complications were seen in nine of those with benign disease. The patients with malignant degeneration were almost exclusively male (97%). Cancer of the esophagus developed in 3 of the men in their early 40s and in one in his 30s. During the same time period, we treated 135 patients with esophageal cancer. Sixty-three (47%) had squamous carcinoma, 43 (32%) had adenocarcinoma of the cardia or lower esophagus, and 29 (21%) had adenocarcinoma in Barrett's esophagus.

Physiologic Testing of Patients with Benign Barrett's Esophagus

Manometry

Esophageal manometry was performed using a single catheter assembly consisting of five water-filled polyethylene tubes with five exit ports located at 5 cm intervals along its length and oriented radially around the circumference of the catheter. The catheter was attached to a pump (Arndorfer Medical Specialties Inc., Greendale, WI) capable of a low perfusion rate with distilled water at 0.6 mL per minute with low compliance, (measured at 100 mmHg in 0.08 seconds during occlusion of the distal side holes). Each perfused channel was linked to a transducer (Statham transducer model P2306, Gould, Cleveland, OH) and the pressure recorded on a Polygraph pen recorder (ES1000, Gould) and stored digitally on a computer (IBM AT, White Plains, NY). This dual record allowed a choice of computerized or manual analysis. Computerized analysis was performed using a dedicated program (ESA/Motility, T. DeMeester, G. Schneider, M. Walker, Creighton University).

TABLE 1. *Barrett's Esophagus: Age and Sex Distribution*

Study Population	n	Mean Age	Age Range	Sex M:F
Patients with Barrett's	76	59	25–89	54:22
No complications	20	51	27–76	14:6
Benign Complications*	27	61	25–89	12:15
Stricture*	20	55	25–85	9:11
Ulceration*	7	60	37–74	3:4
Dysplasia*	11	58	27–74	6:5
Malignant Complications	29	63	36–79	28:1
Adenocarcinoma	28			
Squamous carcinoma	1			

* Note that nine patients (mean age, 46 years) had multiple benign complications.

In the fasting patient, the catheter was introduced through the nose into the stomach and pulled back stepwise across the gastroesophageal junction to obtain a pressure profile of the lower esophageal sphincter.[9] The upper and lower border of the lower sphincter, the respiratory inversion point, and its height above gastric baseline were defined. From these measurements the sphincter's pressure, overall length, and abdominal length, that is, the length below the respiratory inversion point, were determined.

Based on the values obtained in 50 normal subjects,[10] a mechanically defective lower esophageal sphincter was defined as one having one or more of the following characteristics: an average resting pressure of less than 6 mmHg, an average length of less than 2 cm, or an average length exposed to the positive-pressure environment of the abdomen of less than 1 cm. These values are below the 2.5th percentile for the normal range of sphincter pressure and overall length and below the 5th percentile for abdominal length.

Esophageal peristalsis was measured by placing the catheter in the body of the esophagus with the proximal port 1 cm below the lower border of the upper sphincter and asking the patient to take 10 dry swallows and 10 swallows of a 5-mL water bolus. The number of interrupted waves, *i.e.*, waves that failed to progress; dropped waves, *i.e.*, waves that failed to occur in a segment; and simultaneous waves over a 5-cm segment, *i.e.*, beginning within 0.25 seconds of each other, were recorded. The median amplitude of contractions was calculated and compared to the 2.5th percentile of the median amplitudes of 50 normal subjects previously studied in our laboratory.[11]

pH Monitoring

Patients were asked to stop all medication for 48 hours before the study and during the monitoring period. Smoking was not allowed. Twenty-four–hour esophageal and gastric pH monitoring was performed using glass electrodes (Model 440 M4, Ingold, Switzerland) and a portable solid-state monitor (Synectics, Irving, TX) capable of storing pH data from two channels, sampled at four-second intervals. The probes were calibrated before and after monitoring using standard buffers at pH 1 and

7. They were introduced so that the tip was 5 cm above the upper border of the manometrically determined lower esophageal sphincter for esophageal placement and 5 cm below the lower border of the lower esophageal sphincter for gastric placement. The patient was sent home and instructed to remain in the upright position until he or she retired for the evening, to avoid strenuous exertion, and to follow a diet sheet restricting him or her to three meals composed of food with a pH between 5 and 6. Only water was permitted between meals. A diary was kept of food and fluid intake, symptoms experienced during the monitoring period, the time when a supine position was assumed in preparation for sleep, and the time of rising in the morning. At the end of the test, the stored data were transferred to an IBM personal computer and analyzed using commercial software (Gastrosoft, Irving, TX).

The cumulative exposure of the esophagus to acid was expressed as the percentage of time the pH was less than 4 during the study period and defined as abnormal when it exceeded 4.4% (95th percentile of normal). The cumulative exposure of the esophagus to alkalinity was expressed as the percentage of time the pH was more than 7 and defined as abnormal when it exceeded 10.5% (90th percentile of normal).[12]

For gastric pH a discriminant analysis of the pH record was used to diagnose the presence of pathologic duodenogastric reflux. A score of 2.2 previously was shown to distinguish between normals and patients with duodenogastric reflux.[13]

Gastric Acid Secretion and Serum Gastrin Levels

Gastric acid secretion before and after pentagastrin injection was measured using a standard aspiration technique in fasting patients.[14] Hypersecretion was defined by a basal acid output (BAO) of more than 5.0 mmol/hr or a maximal acid output (MAO) of more than 30 mmol/hr. Serum gastrin levels were measured in each patient by radioimmunoassay and recorded in pg/L.

Gastric Emptying Scans

Gastric emptying scans were performed in patients with benign disease using a standard meal of radiolabeled Tc-oatmeal.[15] The percentage of radioactive emission from the stomach was recorded at 15-minute intervals and the decline in the radioactive emission was compared to the decline in 30 control subjects previously studied in our laboratory.[15]

Histopathology

Benign Barrett's esophagus. Biopsies were obtained at endoscopy, with the number per visit ranging from 4 to 48. The diagnosis of Barrett's esophagus was made only when biopsies contained specialized columnar epithelium. The presence of junctional or fundic-type epithelium was recorded but not used to make the diagnosis. Dysplasia was diagnosed according to guidelines proposed by the Inflammatory Bowel Disease-Dysplasia Morphology Study Group.[16] Under these guidelines, low-grade dysplasia was characterized by glands lined by cells with enlarged hyperchromatic nuclei and nuclear crowding with stratification. High-grade dysplasia was characterized by nuclear stratification extending to the luminal surface of glands, marked nuclear pleomorphism, or loss of nuclear polarity. Biopsies were graded as indefinite for dysplasia if there were some cytologic changes, as described above in the presence of florid acute inflammation.

Malignant Barrett's esophagus. In resected specimens with carcinoma, the depth of invasion was described in relation to the standard anatomic landmarks: intramucosal carcinoma if it penetrated the glandular basement membrane but was limited by the muscularis mucosae, intramural carcinoma if it penetrated the muscularis mucosae but not the muscularis propria, and transmural carcinoma if it penetrated the muscularis propria (Fig. 1).

Lymph nodes were dissected carefully from all *en bloc* specimens and assigned to one of the following groups: subcarinal, inferior paraesophageal, parahiatal, around the resected left gastric artery, around the resected splenic artery, and adjacent to the hepatic and celiac arteries. Lymph nodes were submitted separately by the surgeon from the porta hepatis, subpancreatic, and paratracheal areas. The relationship of the involved lymph nodes to

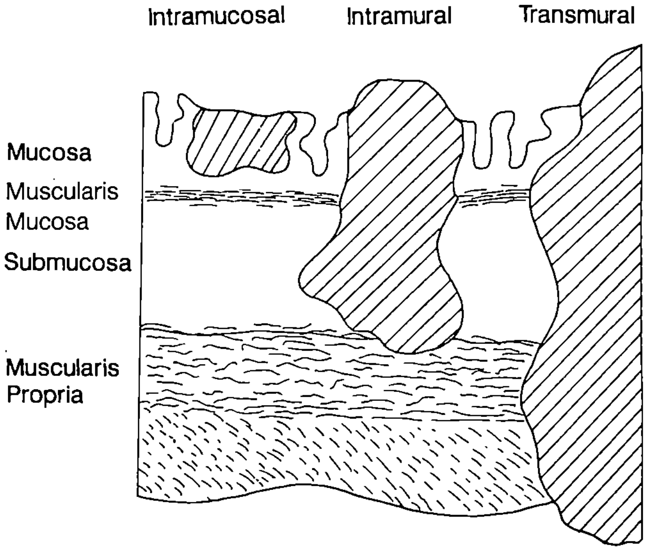


FIG. 1. Staging of the primary tumor according to depth of invasion using standard anatomic landmarks: intramucosal carcinoma if it penetrated the glandular basement membrane but was limited by the muscularis mucosae, intramural carcinoma if through the muscularis mucosae but not through the muscularis propria, transmural if through the muscularis propria.

primary tumor was classified as peritumoral when the nodes were within 5 cm of the epicenter of the tumor, regional when they were contained in the *en bloc* resection but beyond 5 cm, and distant when submitted by the surgeon from areas peripheral to the *en bloc* dissection. The possibilities for the extent of the primary lesion and lymph node involvement are listed in Table 2.

Histologic parameters evaluated were tumor grade, growth pattern, and the presence of squamous and neuroendocrine differentiation. Tumors with well-defined glands were graded as well differentiated; all others were deemed poorly differentiated. Growth pattern was classified as either expanding (well circumscribed, pushing margin) or infiltrative (diffuse permeation of tissue). Neuroendocrine differentiation was suspected if there were sheets or large nests of tumor cells with round nuclei and stippled chromatin; it was confirmed by immunohistochemical stains for chromogranin A and neuron-specific enolase. For immunostaining primary antibodies to neuron-specific enolase and chromogranin A (Biogenex) were applied and an avidin-biotin-peroxidase method was used for immunohistochemical development. Positive controls were represented by unrelated tumors known to contain the appropriate antigens. Substitution of rabbit immunoglobulin for the primary antibodies provided negative controls.

Carcinoembryonic Antigen (CEA)

Carcinoembryonic antigen in the serum of patients with malignant disease was measured using the Abbott EIA method. The normal value for healthy adults is less than 5 ngr/mL. Tissue from adenocarcinomas arising in Barrett's esophagus was tested for expression of CEA using methods similar to those described above, except that the primary antibody was a polyclonal antibody directed against CEA (DAKO, Carpinteria, CA).

Treatment

Benign Disease

Medical therapy consisted of conservative measures, antacid medication, and H2 receptor antagonists. Indications for antireflux surgery were persistent symptoms, including evidence of aspiration, or the presence of stricture, ulcer, or hemorrhage. The choice of antireflux operation was based on the strength of esophageal contractions and the length of the esophagus. A short Nissen fundoplication (1.5 to 2 cm) over a 60-Fr bougie was used in patients with adequate contractility and length of the esophageal body.[17] In patients with inadequate contractility, a Belsey partial fundoplication was done and combined with a Collis gastroplasty when esophageal shortening was present. A resection was considered in patients with high-grade dysplasia or those with poor contractility and a severe stricture.[18]

TABLE 2. *Adenocarcinoma in Barrett's Esophagus: Classification by Depth of Invasion and Lymph Node Metastases*

Primary Tumor	Lymph Nodes
0. *In situ* carcinoma	A. No metastases
1. Intramucosal carcinoma	B. Peritumoral metastases
2. Intramural carcinoma	C. Regional metastases
3. Transmural carcinoma	D. Distant metastases

Malignant Disease

The decision for a curative resection of a carcinoma in Barrett's esophagus was based on the age (75 years or younger) and physiologic fitness (cardiovascular and pulmonary status) of the patient, the preoperative assessment of tumor spread, and intraoperative staging.[19,20] Preoperative staging was done by computed tomographic (CT) scanning for lymph node involvement and distant organ metastases and by endoscopic assessment and measurement of the primary tumor. Patients with tumor measuring 5 cm or less in length and involving less than one half of the esophageal circumference on endoscopy, and no evidence of lymph node enlargement or distant metastasis on CT scan were considered for curative resection. Intraoperative staging was used to switch from a curative to a palliative procedure.[19] The indications to switch were a tumor that could not be resected, cavitary spread, tumor penetration of the mediastinal pleura, distant metastases, obvious multiple node involvement, or microscopic node involvement at the periphery of the resection: paratracheal, subpancreatic, or porta hepatis nodes.

A curative operation consisted of an *en bloc* resection of the distal esophagus, proximal stomach, spleen, and splenic artery, together with the following nodal groups: subcarinal, inferior paraesophageal, parahiatal, left gastric, celiac, hepatic and splenic artery nodes, and subpancreatic. Gastrointestinal continuity was re-established using a colon interposition, as previously described by our group.[18] Patients who were not candidates for curative surgery and who had dysphagia had a palliative transhiatal resection,[21] with esophagogastrostomy in the neck.

Follow-up

Patients with benign disease were seen at yearly intervals, or more often if necessary, for endoscopic surveillance and to assess their response to therapy. Functional results were classified as good: asymptomatic, or with inconsequential symptoms requiring no therapy; fair: improved, but with symptoms and/or endoscopic findings requiring intermittent therapy (antireflux medication or dilatation); poor: unimproved or worse. The median duration of follow-up in benign disease was 3.0 years, with a range of 1 to 12 years. In malignant disease patients were seen at 3-month intervals for 3 years and annually thereafter, and no patients were lost to follow-up.

Statistical Methods

Nonparametric tests of comparison (Wilcoxon rank-sum test) and the Fisher's exact test of proportion were used to compare groups with benign disease. For patients who had a curative resection for malignancy, survival was calculated using the Kaplan–Meier actuarial method.[22] After palliative resection the median survival in months was calculated.

Results

Physiologic Tests in Benign Barrett's Esophagus

Esophageal manometry. Esophageal manometry and pH monitoring were performed in 41 of the patients with benign disease. The lower esophageal sphincter was mechanically defective in 37 patients (90%) due to a low pressure alone or in combination with a short overall or abdominal length in 29, and a short abdominal length alone in 8. There was no difference in the prevalence of a mechanically defective sphincter between those with or without complications. The median value for each component of the sphincter was less than the 2.5th percentile of normal (Fig. 2).

The amplitude of esophageal contractions in patients with Barrett's esophagus was normal in the proximal two fifths of the esophagus, but markedly reduced in the distal three fifths compared to normal volunteers (Fig. 3). There was also a high prevalence of simultaneous, dropped, and/or interrupted waves in the distal three fifths of the esophagus (Fig. 4). Thirty-four of forty-one patients (83%) with Barrett's esophagus had peristaltic failure in the distal esophagus due to inadequate contractility and/or abnormalities of wave progression. The frequency of the motility abnormalities in the body of the esophagus was similar in those with or without complications.

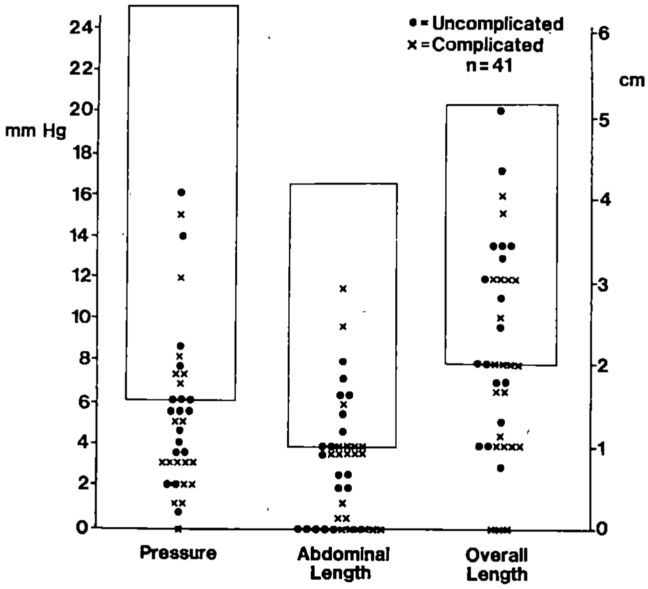


FIG. 2. Distribution of lower esophageal sphincter pressure, abdominal length, and overall length in 41 patients with Barrett's esophagus. ● = uncomplicated Barrett's. X = complicated Barrett's. The boxes represent the normal range (2.5th to 97.5th percentile for pressure and overall length, 5th to 95th percentile for abdominal length).

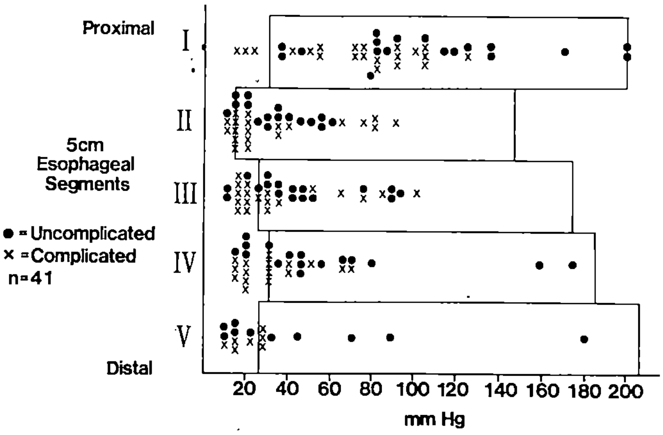


FIG. 3. Distribution of amplitude of esophageal contractions in 41 patients with Barrett's esophagus. ● = uncomplicated Barrett's. X = complicated Barrett's. The boxes represent the normal range (2.5th to 97.5th percentile) of amplitude for each 5-cm segment of the esophageal body. In patients with short esophagi, only three or four segments were able to be measured.

Twenty-four-hour esophageal pH monitoring. Compared to normal values, esophageal acid exposure was increased in 38 (93%) and alkaline exposure in 14 (34%) of the 41 patients tested. In two of the three patients with normal acid exposure, an increased alkaline exposure was documented. The prevalence of increased acid exposure in patients with complications was the same as in those without complications, whereas the prevalence of in-

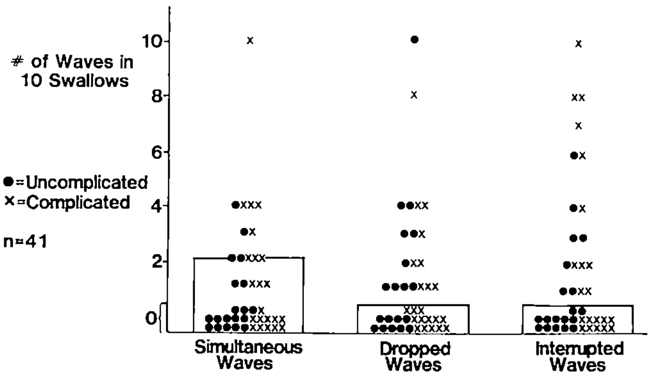


FIG. 4. The frequency of simultaneous, dropped, or interrupted esophageal contractions in 41 patients with Barrett's esophagus. ● = uncomplicated Barrett's. X = complicated Barrett's. Boxes represent the range of normal.

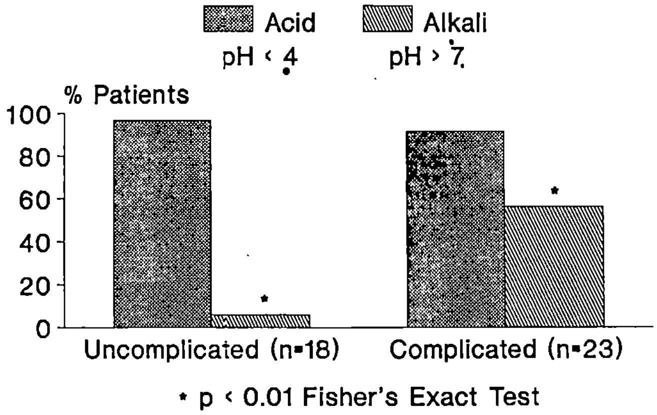


FIG. 5. The prevalence of abnormal esophageal acid and alkaline exposure in patients with or without complications of Barrett's esophagus.

creased alkaline exposure was significantly higher in those with complications (Fig. 5). This observation of a similar prevalence of acid exposure and different alkaline exposure was also true for the mean percentage time the pH was less than 4 or more than 7 (Figs. 6 and 7). Of the 14 patients who had increased esophageal alkaline exposure, 13 (93%) had complications. Of the 27 patients with normal alkaline exposure, 12 (44%) had complications. The likelihood of a specific complication occurring in a patient with increased alkaline exposure is shown in Table 3.

Twenty-four-hour gastric pH monitoring. Discriminant analysis of the 24-hour gastric pH data showed an abnormal score for duodenogastric reflux in 10 of 24 patients tested. Of the 10 patients with documented duodenogastric reflux, five had increased esophageal alkaline exposure. Of the 14 patients shown not to have duodenogastric reflux, none had increased esophageal alkaline exposure. The prevalence of duodenogastric reflux was higher in patients with complications of Barrett's esophagus (p < 0.05; Fig. 8).

Serum gastrin levels. Fasting serum gastrin levels were measured in 22 patients; 11 had normal and 11 increased esophageal alkaline exposure. The mean gastrin level (± SEM) in patients with increased esophageal alkaline exposure was 59 (± 11) pg/mL compared to 35 (± 7.5) pg/mL in those with normal alkaline exposure (p < 0.05).

Gastric secretion studies. Gastric hypersecretion was documented in 10 of 23 patients (44%) tested. Table 4 shows that the mean value of acid secretion was similar

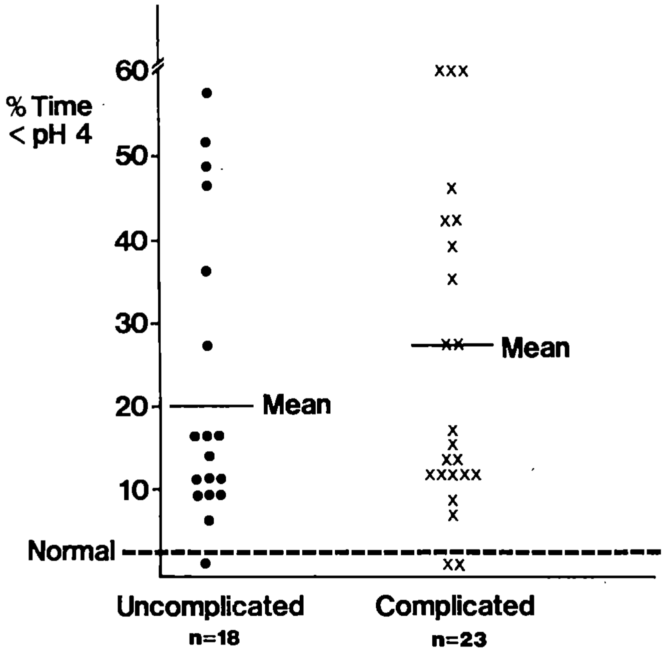


FIG. 6. Distribution and mean value of esophageal acid exposure (percentage of time pH < 4) in patients with or without complications of Barrett's esophagus (p < 0.05).

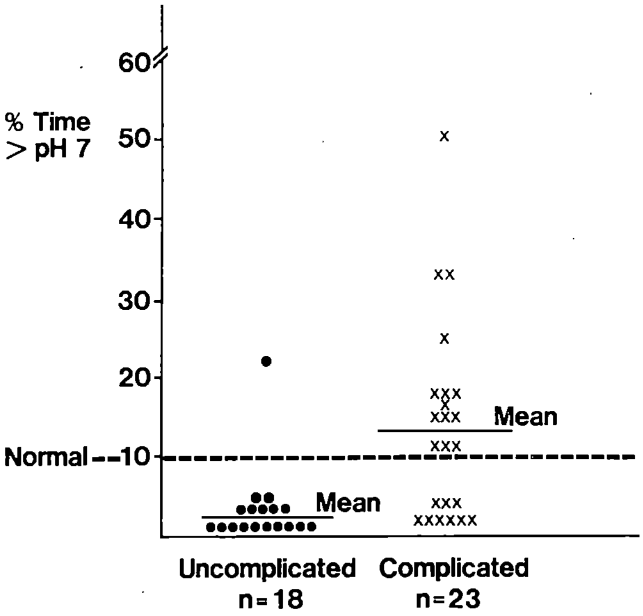


FIG. 7. Distribution and mean value of esophageal alkaline exposure (percentage of time pH > 7) in patients with or without complications of Barrett's esophagus (p < 0.01).

TABLE 3. *The Relationship Between Complications in Barrett's Esophagus and Esophageal Alkaline Exposure*

Complication		Increased Alkaline Exposure (n = 14)	Normal Alkaline Exposure (n = 27)	Fisher Test
Stricture	18*	11/14 (79%)	7/27 (26%)	p < 0.01
Dysplasia	11	6/14 (43%)	5/27 (19%)	p = 0.09
Ulcer	7	3/14 (21%)	4/27 (15%)	p = 0.33
Any above	25	13/14 (93%)	12/27 (44%)	p < 0.001

* Two patients with stricture did not have 24-hour esophageal pH monitoring.

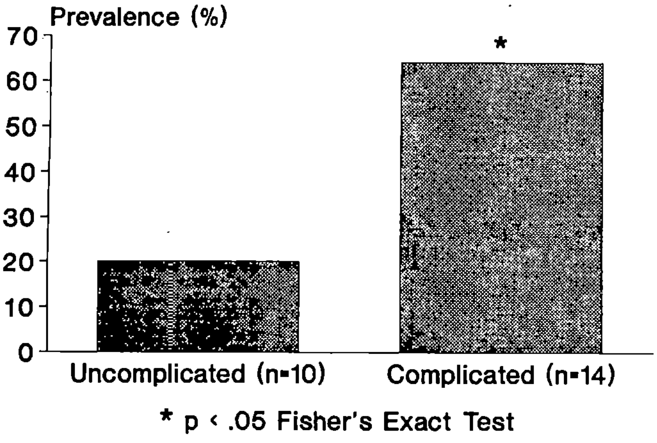


FIG. 8. The frequency of duodenogastric reflux in patients with or without complications of Barrett's esophagus ($p < 0.05$).

in patients with and without complications of Barrett's esophagus.

Gastric emptying. Gastric emptying scans were reported abnormal in 17 of 32 (53%) patients tested, with delayed emptying in 13 and rapid in 4. Gastric emptying was similar in those with normal or increased alkaline esophageal exposure. Figure 9 illustrates that the mean gastric emptying rate in the 26 patients whose curves were available was initially slower in those with complications of Barrett's esophagus. There was no statistically significant difference in the retention half life (T½) between the two groups, and both curves were within the normal range.

Pathology in Benign Barrett's Esophagus

By definition the 47 patients with benign Barrett's esophagus had specialized columnar epithelium in the lower esophagus. In seven patients there was also junctional-type epithelium and in six fundic-type epithelium was evident. Paneth cells were identified in the specialized epithelium of six patients and neuroendocrine cells were present in four. Eleven of the patients with benign Barrett's esophagus showed evidence of dysplasia, low grade in nine and high grade in two. Two patients had biopsies indefinite for dysplasia. The dysplastic changes always were localized to specialized columnar epithelium. In five patients dysplasia was seen concomitantly with stricture and in two, with an ulcer.

TABLE 4. *Gastric Secretion Studies in Patients with Benign Barrett's Esophagus*

Study	Uncomplicated Barrett's (n = 8)	Complicated Barrett's (n = 15)	p Value
Prevalence of hypersecretion	5/8	5/15	NS
Basal acid output (mmol/hour)	7.1 ± 5.8	3.2 ± 2.5	NS
Maximum acid output (mmol/hour)	28 ± 14	18 ± 9.4	NS

NS, not significant.

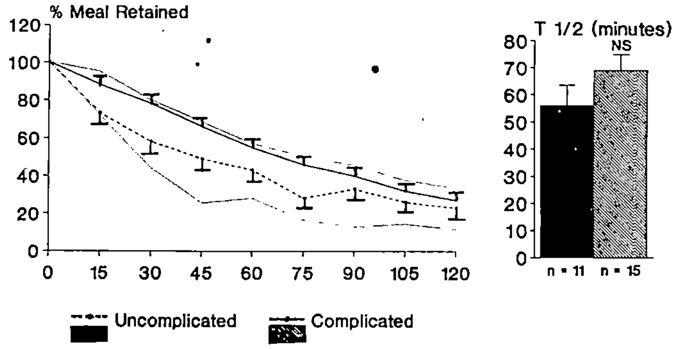


FIG. 9. The gastric emptying rate in 26 patients with or without complications of Barrett's esophagus. The fine dotted lines represent the 10th to 90th percentiles of normal. The mean $T\frac{1}{2}$ is illustrated in the bar graph. There was no difference between the groups ($p > 0.05$).

Results of Therapy in Benign Barrett's Esophagus

Antireflux surgery was performed in 35 patients: a Nissen fundoplication in 31 (combined with a proximal gastric vagotomy in 6), a Belsey partial fundoplication in 3, and a Collis gastroplasty combined with a Belsey partial fundoplication in 2. Six patients had an esophageal resection. In four patients the indication for resection was an esophageal stricture with inadequate esophageal contractility and persistent dysphagia after dilatation, and in two patients the indication was the presence of high-grade dysplasia. One of the patients with a stricture had an associated ulcer that penetrated into the mediastinum and two had low-grade dysplasia. Neither of the latter had intramucosal carcinoma in the resected specimen, whereas it was discovered in one of the specimens resected for high-grade dysplasia.

The symptomatic results of surgical therapy are shown in Table 5. Four patients who had relief of heartburn and dysphagia continue to have abdominal pain, nausea, and bilious vomiting after antireflux surgery, suggesting persistence of duodenogastric reflux. Three of the four were tested for duodenogastric reflux. All three were positive and subsequently had bile diversion procedures. Three patients required continuation of acid suppression ther-

TABLE 5. *Symptomatic Results of Surgical Therapy*

Procedure	n	Good	Fair	Poor
Nissen	30	23	6	1
Belsey	3	3	0	0
Collis–Belsey	2	1	1	0
Total	35	27 (77%)	7 (20%)	1 (3%)
Resection	6	3	3	0

apy, one for recurrent heartburn and two for symptomatic gastritis associated with gastric hypersecretion. Only 1 of the 20 stricture patients required postoperative dilatations and no strictures developed after surgery. All six of the Barrett's ulcers treated by antireflux operation healed on endoscopic follow-up and have not recurred. Overall 77% of the patients had a good result after antireflux surgery.

Carcinoma has not develped in any of the 35 patients who underwent antireflux surgery. Of the nine patients with dysplasia, none has progressed and one has persisted as high grade. Neither the total length of the Barrett's esophagus nor the size of the dysplastic area appears to have changed during a mean follow-up of 3 years, totalling 123 patient years.

In six patients surgery was not performed. In three the operative risk was high because of age or poor cardiovascular condition, and in three the patients chose not to have an operation. In these patients symptoms persisted despite the continuation of therapy with H2 receptor antagonists.

Surgical Resection for Carcinoma in Barrett's Esophagus

A curative resection was performed in 15 patients with adenocarcinoma. One of the two patients who had an esophagectomy for high-grade dysplasia had intramucosal carcinoma in the specimen, increasing the number of patients with early adenocarcinoma to 16. These patients were all less than 75 years of age, with good cardiorespiratory function. One patient with an intramural tumor died while hospitalized, resulting in a hospital mortality rate of 6%.

Palliative surgery was performed in 10 patients because of extensive local disease. In four patients no resection was performed because of extensive local disease in each along with the intraoperative discovery of undiagnosed liver metastases in two. In none of these patients did CT scanning detect the mediastinal or liver involvement.

Survival After Resection for Carcinoma

An actuarial survival curve was calculated for the 15 patients who underwent a curative resection and one patient who had intramucosal carcinoma discovered in the specimen resected for high-grade dysplasia. Two years after resection, the survival rate was 77% and after 5 years it was 53% (Fig. 10). Table 6 shows the relationship of the depth of the primary tumor and lymph node involvement to survival. Four of the five patients with intramucosal carcinoma are alive 20, 24, 39, and 105 months after resection. One died at home from an acute pulmonary embolus 2 months after surgery. In contrast the median survival time for patients after palliative resection or no resection was 12 months.

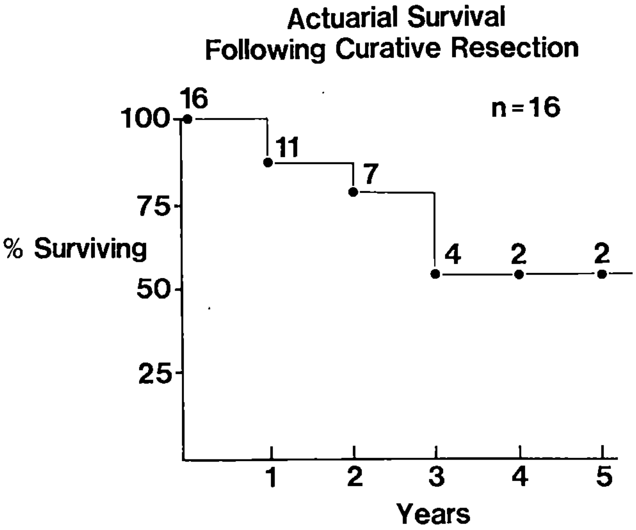


FIG. 10. The actuarial survival times of patients with adenocarcinoma in Barrett's esophagus after curative resection, calculated by the Kaplan-Meier method, illustrating a 77% 2-year survival rate and 53% 5-year survival rate. The numbers on the curve refer to the number of patients alive at the start of each year.

Histopathology of Carcinoma in Barrett's Esophagus

Of the 29 carcinomas arising in Barrett's esophagus, 25 were resected and available for pathologic assessment. All 25 specimens contained specialized columnar epithelium adjacent to the adenocarcinoma. Six of the twenty-five also contained junctional-type epithelium and four contained fundic-type epithelium. In every specimen there was low-grade dysplasia adjacent to the tumor, and in 13 specimens high-grade dysplasia also could be identified (Fig. 11). The dysplastic changes were confined to the specialized columnar epithelium, except for one specimen in which dysplastic cells occurred in fundic-type Barrett's epithelium.

The pathologic features for each cancer in which an *en bloc* resection was done for cure are summarized in Table 7. There are several salient observations to be made. (1) Among 16 specimens the tumor was intramucosal in 5, intramural in 7, and transmural in 4. (2) The extent of lymph node involvement was related to the extent of the primary tumor. Lymph node involvement was not seen with intramucosal carcinoma. In the seven patients with intramural tumor, five had positive nodes. They were few and peritumoral in four patients, and many and regional in one patient. All four patients with transmural tumor had peritumoral lymph node metastases and two had extension to regional and distant nodes. The latter were discovered at operation after the opportunity to convert to a palliative resection had passed. None of the 15 patients who had an *en bloc* resection for cure had positive nodes along the splenic artery. (3) Differentiation and growth

TABLE 6. *Outcome After Resection for Cure*

		Years Follow-up				
Stage	n	<1	1–2	2–3	3–4	4–5
Intramucosal* nodes negative	5	1 D	2 A	—	1 A	1 A
Intramural nodes negative	2	1 A	—	—	1 A	—
Intramural nodes positive	5	1 A, 1 D	—	1 A, 1 D	—	1 A
Transmural nodes positive	4	1 A	1 D	1 A, 1 D	—	—

* Includes one patient who had an esophagectomy for high-grade dysplasia, in whom intramucosal carcinoma was discovered in the resected specimen.

A, alive; D, dead.

patterns were variable. Eight of the 16 tumors were well differentiated; eight were poorly differentiated. Of the 11 intra- or transmural tumors, six had an expanding growth pattern, while five were infiltrative. None of the tumors had areas suggesting neuroendocrine differentiation. Three contained signet cells.

Pathologic features for each cancer in which a palliative resection was done are summarized in Table 8. Among the 10 specimens three tumors were intramural and seven were transmural. The limited nature of the resection prevented complete evaluation of lymph node involvement. Eight patients had lymph nodes sampled at surgery; all contained metastases. One tumor consisted entirely of squamous carcinoma and another had areas of squamous differentiation. No tumor contained signet cells. One tumor had neuroendocrine differentiation confirmed by a positive stain for chromogranin A and neuron-specific enolase.

Carcinoembryonic Antigen (CEA)

Serum CEA was measured initially in 23 patients with carcinoma in Barrett's esophagus and followed serially in 12. One of these patients had an initial elevation that returned to normal after resection. Of the remaining 11 patients, subsequent CEA levels increased to more than normal values in seven, all of whom developed metastases. In five of these patients, the increase preceded the clinical detection of metastases by a period of 2 to 12 months. This gave a sensitivity for detecting occult recurrent disease of 71% and a predictive value for a positive test of 100%. In all others the CEA remained static, with no evidence of recurrent disease.

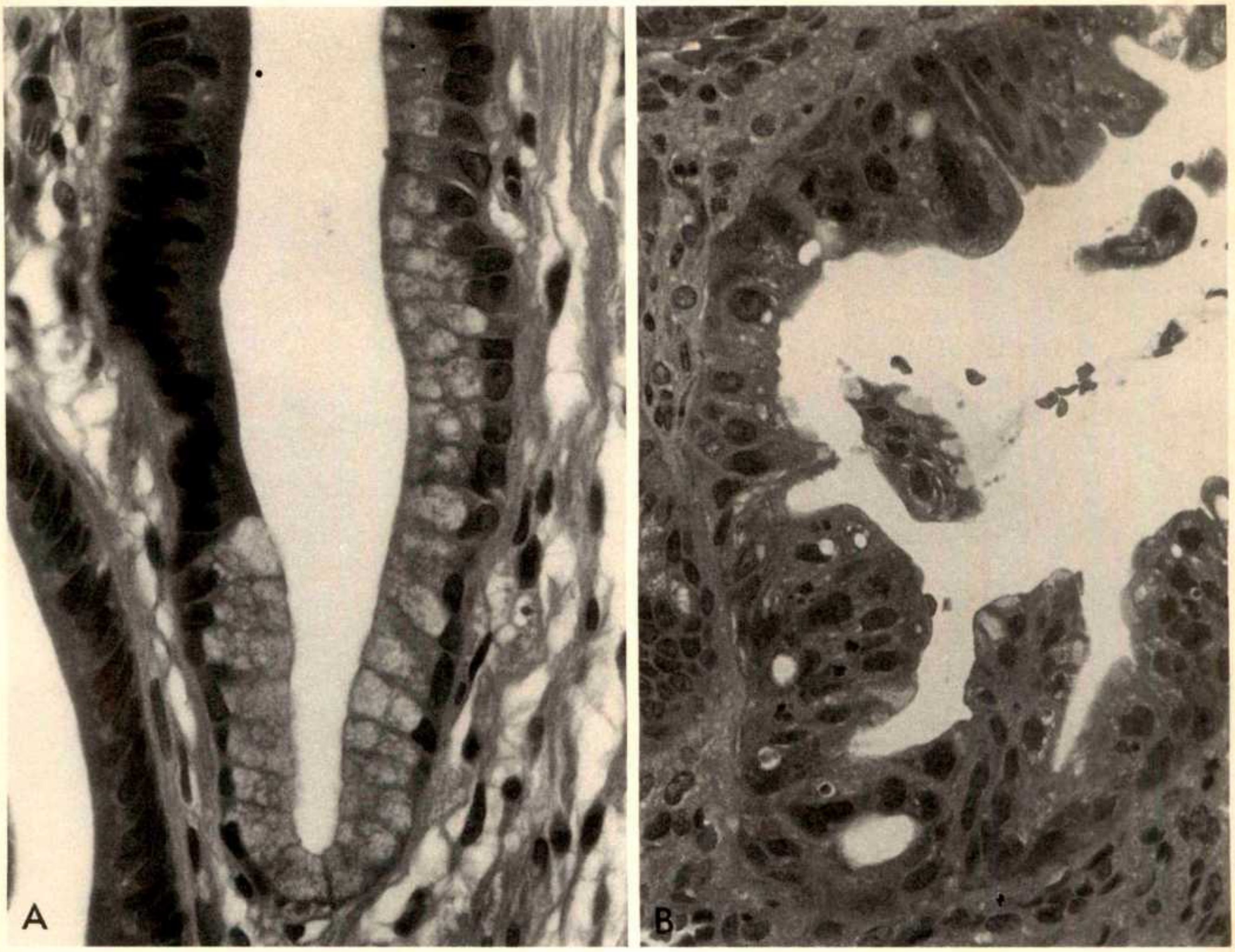
Carcinoembryonic antigen was demonstrated in 15 of 17 tumors tested. The negative tumors were a squamous cell carcinoma and a poorly differentiated adenocarcinoma. The latter tumor was from a patient who presented with advanced disease but a normal serum CEA. Barrett's esophagus adjacent to the tumor stained only occasionally (3 of 17 patients) even when dysplastic. Intramucosal carcinoma, on the other hand, invariably expressed CEA.

Discussion

This study shows that Barrett's esophagus is associated with end-stage reflux disease characterized by high esophageal acid exposure, gastric hypersecretion, and the loss of esophageal function; that complications associated with Barrett's esophagus, *i.e.*, stricture and possibly ulcer and dysplasia, are increased with abnormal esophageal alkaline exposure secondary to duodenogastric reflux; and that the patient with early malignant degeneration can be cured by surgical resection.

Ninety-three per cent of patients with benign Barrett's esophagus had increased esophageal exposure to acid gastric juice. The mean percentage time esophageal pH of less than 4 was six times normal.[12] This is even higher than that reported for stricture or esophagitis.[11] This exposure was due to the 90% prevalence of a mechanically defective sphincter and a 44% prevalence of gastric hypersecretion. Because a mechanically defective sphincter was seen in 50% of reflux patients without esophagitis, stricture, or Barrett's esophagus, it may be the primary cause for increased esophageal acid exposure in patients with Barrett's esophagus rather than resulting from the exposure.[11] On the other hand, there is evidence that the loss of esophageal contractility and wave progression observed in 83% of our patients results from organ damage secondary to the increased esophageal exposure to gastric juice.[23,24] These findings should encourage antireflux surgery before the loss of esophageal body function. Indeed the 77% symptomatic improvement observed after antireflux surgery in this study is less than the 91% observed in patients who had antireflux surgery for gastroesophageal reflux disease not complicated by stricture or Barrett's esophagus.[18]

An important observation was that 93% of patients with increased esophageal alkaline exposure had complications of their Barrett's esophagus, *i.e.*, stricture, ulcer, or dysplasia. This was further supported by the finding that the mean percentage of time the esophagus was exposed to a pH more than 7 in patients with complications was 13.5% compared to 2% in those without complications. Although



FIGS. 11A–D. (A) Low-grade dysplasia occupying part of a gland. There is nuclear crowding, elongation, and stratification (×650). (B) High-grade dysplasia, with nuclear pleomorphism and more pronounced stratification. (×650) (C) Intramucosal carcinoma, showing irregular cords of cells invading the lamina propria (×165). (D) Intramucosal carcinoma showing the malignant characteristics of the glands (×650).

complications were seen in patients with increased esophageal acid exposure alone, the prevalence of increased acid exposure and the mean percentage of time the esophagus was exposed to pH less than 4 were similar in those with or without complications. Furthermore patients without complications had a prevalence of hypersecretion and a degree of acid secretion that were similar to those with complications, suggesting that exposure to a component of gastric juice other than acid was important in the development of complications.

Our studies indicated that the source of the increased esophageal alkaline exposure was duodenal juice refluxed into the stomach and then into the esophagus. Twenty-four–hour gastric pH monitoring documented duodenogastric reflux in 42% of the patients with Barrett's esophagus and one half of these had increased esophageal alkaline exposure. Increased esophageal alkaline exposure was never seen in the absence of duodenogastric reflux. In addition patients with increased esophageal alkaline exposure had higher serum gastrin levels than did those with normal alkaline exposure, a finding consistent with alkalinization of the stomach by duodenogastric reflux and subsequent alkaline gastroesophageal reflux. This also was reflected in the gastric secretion studies in which the prevalence of hypersecretion and degree of acid secretion were similar in patients with and without complications. It may be that this finding represents the extreme and that duodenal juice is in the esophagus even when the esophageal pH is less than 7.

Our studies show that malignancy arising in Barrett's esophagus is curable by surgical resection if detected at an early stage. The potential for cure is highest for intramucosal carcinoma. Four of five patients with this lesion are alive after resection. Of the seven patients with intra-

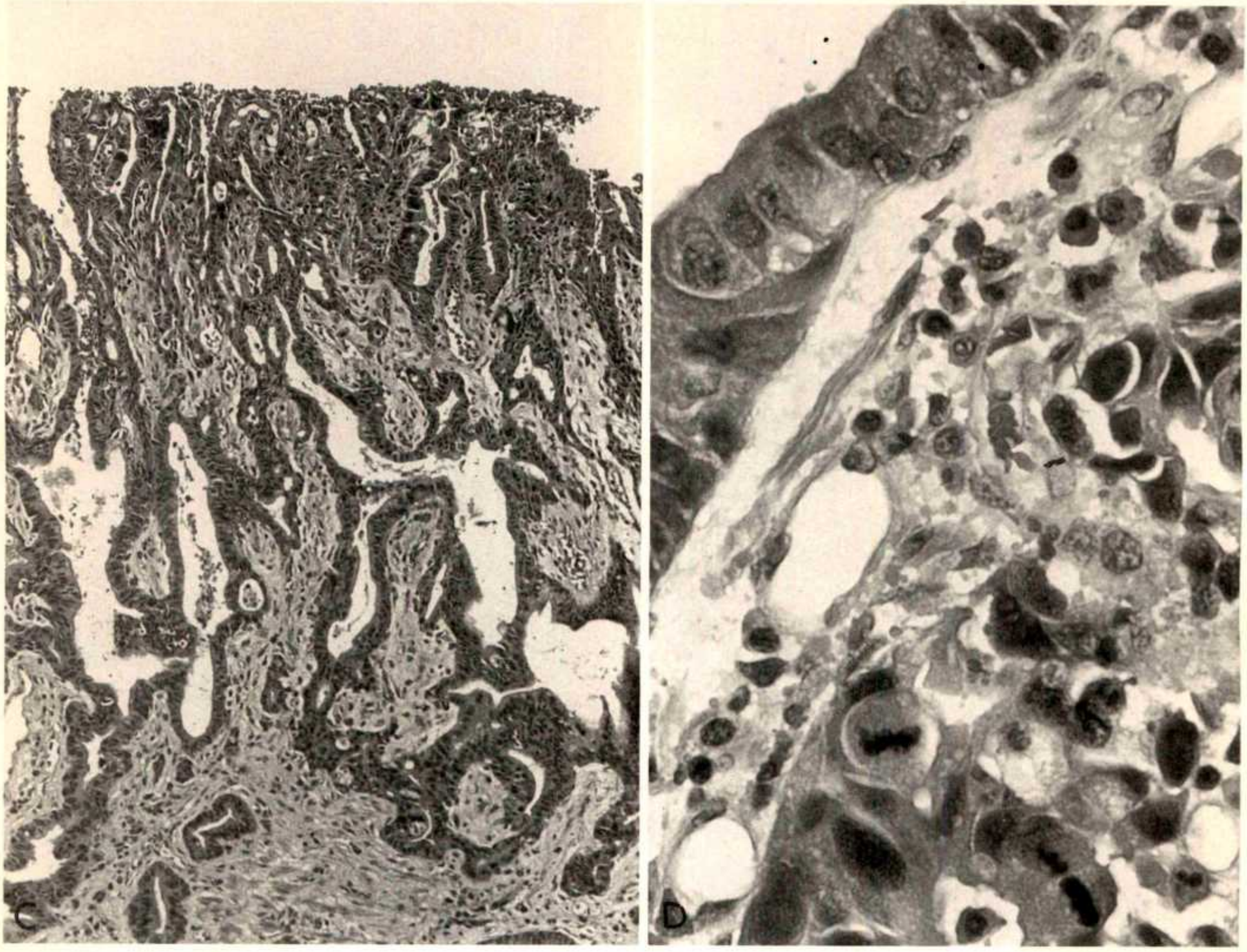


FIG. 11. (*Continued*)

mural tumor, five are alive and two of four patients with transmural tumor are alive.

Another important determinant of survival was the presence of lymphatic metastases. None of the patients with uninvolved nodes has died of cancer after a curative resection. Peritumoral lymph node metastases are compatible with long-term survival when the nodes are removed as part of an *en bloc* resection. Four of seven such patients are alive and free of disease after 1, 15, 29, and 92 months. There was no correlation between grade of differentiation or growth pattern and survival.

Clinically an intramucosal carcinoma is usually discovered in a patient without an endoscopically visible tumor when biopsy shows malignancy but no submucosal invasion. Because intramural invasion is difficult to exclude in biopsy material, we rely on the absence of a visible mass to suggest the diagnosis of intramucosal carcinoma. Based on the finding that none of the five intramucosal carcinomas were associated with lymph node metastases, we recommend that these lesions should be treated by esophagectomy without *en bloc* dissection. Intramural and transmural carcinomas are recognized endoscopically as small tumors, usually less than 5 cm in length, involving less than one half of the esophageal circumference. They are differentiated only by examining the resected specimen. Both are frequently accompanied by lymph node metastases, but the involved nodes associated with intramural tumors usually are confined to the vicinity of the primary tumor. In contrast the lymph node metastases associated with transmural tumors are more extensive with involvement of regional nodes, with the exception of splenic artery nodes. For this reason we recommend *en bloc* resection with splenic preservation for these lesions. Endoscopic ultrasound may help to distinguish intramucosal from intramural carcinomas, and intramural from transmural carcinomas.

TABLE 7. *Pathology of Adenocarcinoma in Barrett's Esophagus Resected for Cure*

Patient	Primary Tumor	Size (cm)	Location of Nodes (#)	Tumor Grade	Growth Pattern
1	Intramucosal	—	*	Well	†
2	Intramucosal	—	None	Well	†
3	Intramucosal	—	None	Well	†
4	Intramucosal	—	None	Well	†
5	Intramucosal	1.5	None	Poor	†
6	Intramural	3	None	Well	Expanding
7	Intramural	2.5	None	Poor	Expanding
8	Intramural	1	Peritumoral (2)	Poor	Infiltrative
9	Intramural	3	Peritumoral (1)	Well	Expanding
10	Intramural	2.5	Peritumoral (1)	Well	Expanding
11	Intramural	0.5	Peritumoral (2)	Poor	Expanding
12	Intramural	3	Peritumoral (2) regional (7)	Poor	Infiltrative
13	Transmural	5	Peritumoral (2)	Poor	Infiltrative
14	Transmural	4	Peritumoral (1)	Poor	Infiltrative
15	Transmural	4.5	Peritumoral (6) regional (7) distant (2)	Poor	Expanding
16	Transmural	2	Peritumoral (5) regional (11) distant (3)	Well	Infiltrative

— No visible tumor.

* Resected for high-grade dysplasia; *en bloc* resection not done.

† Growth pattern cannot be assessed for intramucosal carcinoma.

The appearance of squamous or neuroendocrine differentiation in Barrett's carcinomas was described previously and is compatible with the multipotentiality of the specialized columnar epithelium. It was suggested that gastrointestinal carcinomas with neuroendocrine areas have a poor prognosis.[25] Indeed our patient with such a tumor had metastases to celiac artery lymph nodes at the time of surgery and experienced bony metastases within 1 year after a palliative resection.

Almost all tumors tested stained positively for CEA. Staining was always seen in intramucosal carcinoma, but almost never in high-grade dysplasia, indicating that the

TABLE 8. *Pathology of Adenocarcinoma in Barrett's Esophagus Resected for Palliation*

Patient	Primary Tumor	Size (cm)	Location of Involved Nodes Sampled (#)	Tumor Grade	Growth Pattern
1	Intramural	1.5	Not sampled	Well	Expanding
2	Intramural	6	Peritumoral (5) regional (5)	Poor	Expanding*
3	Intramural	7	Peritumoral (1) regional (1) distant (1)	Poor	Infiltrative†
4	Transmural	9	Not sampled	Poor	Infiltrative
5	Transmural	4	Peritumoral (5)	Well	Infiltrative
6	Transmural	4	Peritumoral (5) regional (1)	Poor	Infiltrative
7	Transmural	2.5	Peritumoral (2)	Poor	Infiltrative
8	Transmural	2.5	Peritumoral (4) regional (3)	Poor	Infiltrative
9	Transmural	8.5	Peritumoral (4) regional (4) distant (2)	Poor	Infiltrative‡
10	Transmural	7.5	Peritumoral (5) regional (4) distant (6)	Poor	Infiltrative

* Squamous cell carcinoma arising in Barrett's esophagus.

† Areas of neuroendocrine differentiation.

‡ Areas of squamous differentiation.

latter may not have assumed fully malignant characteristics. Serum CEA levels are valuable in following patients after resection because an elevation frequently precedes, and is always indicative of, recurrent tumor.

Although high-grade dysplasia is an indication for esophagectomy,[26] we prefer to proceed with esophagectomy if intramucosal carcinoma is present. Esophagectomy is a formidable undertaking and waiting until biopsies show such change has not compromised survival. This position requires a compliant patient, a compulsive endoscopist, and a competent pathologist working in cooperation with the surgeon.

This study again shows the malignant potential of Barrett's esophagus and supports the need for surveillance. This will lead to the detection of earlier tumors that can be cured by surgical resection. The extent of resection should be adapted to the extent of disease present: esophagectomy for intramucosal disease, *en bloc* esophagectomy with splenic preservation for intramural and transmural disease, and palliative resection for advanced disease.

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DISCUSSION

DR. DAVID SKINNER (New York, New York): I enjoyed Dr. DeMeester's paper and particularly appreciated his excellent physiologic data on this problem.

I would like to emphasize one point in particular here. Tom's data show that early Barrett's carcinoma is a curable disease, and there is a controversy in the gastrointestinal literature about the value of ongoing surveillance of this condition by cytology or by endoscopy.

We have had seven patients with early Barrett's carcinoma detected more than 5 years ago and six of the seven patients are 5-year survivors and none has recurrent carcinoma. I think the data are now becoming overwhelming that this is a curable disease if it is found at an early stage.

A persisting controversy is how to treat patients with high grade dysplasia. I would like to ask Dr. DeMeester how he approaches that problem.

Next month at the Society of Surgery of the Alimentary Tract meeting we will report a series of patients with high-grade dysplasia without a preoperative diagnosis of invasive carcinoma who were treated by resection. One half of them had invasive carcinoma in the resected specimen, so I think that surveillance is worthwhile and aggressive treatment of this disease in the early stage of malignancy will save some patients.

DR. F. HENRY ELLIS, JR. (Burlington, Massachusetts): I would like to direct my comments and a few questions to perhaps the most serious complication, namely, the development of carcinoma.

I am indebted to Dr. Williamson and Dr. Strice for accumulating these data. We have had, during the past 10 years or so, 241 patients with Barrett's esophagus and a 27% prevalence rate of cancer, which really reflects our patient referral patterns rather than the true risk. Approximately 150 patients were followed endoscopically. We calculated a risk factor of one case of cancer in 99 years of follow-up, which is a somewhat higher risk than reported by others, particularly the Mayo Clinic group. I wonder if Dr. DeMeester has data that confirm or negate this risk factor that we have calculated.

We agree with him that the operability and resectability rates are much higher for cancer developing in Barrett's esophagus than in other types of esophageal cancer, probably because these patients are followed more closely.

On the other hand, if one considers only those patients who survive resection, our overall 5-year survival rate of 23% is no higher than it is for cancers in other locations or of other cell types.

I am a little concerned about the 53% 5-year survival rate that Tom mentioned, and I am not sure that you can use the Kaplan–Meier actuarial technique to evaluate results on so few patients. I think the total was 16 and there were only two patients who were available to be studied at 5 years, and we have not been able when we subdivide our group into the various stages to come up with 5-year data, so that the 3-year data are shown here. I agree that the early stages yield pretty good results and are probably comparable to the uncertain data of 53% that he gives.

The implication of Tom's paper is that bigger is better and a very, very radical operation is the answer to the problem. I seriously question whether that is true for these patients of ours with good 3-year survival rates in the early stages who were treated by a standard, fairly limited resection.

I wonder if he would comment on this aspect of the problem.

DR. JAMES B. D. MARK (Stanford, California): I have a question that is a bit on the other end of the spectrum. Is Barrett's esophagus ever reversible? If it is, we can save these operations for cancers that Dr. Skinner has noted are very hard to detect before resection of the esophagus. If we had a simpler operation that would prevent the recurrence of cancer in otherwise uncomplicated Barrett's esophagus, it would be nice.

I wonder if Dr. DeMeester would address that question.

DR. ROBERT E. CONDON (Milwaukee, Wisconsin): I would like to open the issue of whether mediastinal node dissection makes a difference in the management of adenocarcinoma of the esophagus, particularly in the context of Barrett's disease.

In our experience, which is of comparable numbers of patients with cancers in Barrett's esophagus and with a comparable Kaplan–Meier actuarial 5-year survival, the major difference is that our patients have all been approached without doing mediastinal or other lymphadenectomy. We have resected all gross disease.

We have, by and large, done this by means of blunt transhiatal esophagectomy. If you can achieve the same results without the node dissection, is it really necessary?

It seems to me that the factors that control the outcome in adenocarcinoma of the esophagus are the stage of the disease at the time the patient comes for treatment and the biology of the tumor in a given patient. Neither of those features is within the control of the surgeon.

DR. JAY L. GROSFELD (Indianapolis, Indiana): Obviously, this is just one of a number of abnormal motility disorders of the embryonic foregut, and the same kind of patients in a younger age group than you are reporting also have a significant degree of delays in gastric emptying. In some instances we have also been able to culture *Campylobacter pylcrium* in patients with Barrett's esophagus.

I wonder if you would address these issues.

PROFESSOR JOHANNES A. MYBURGH (Johannesburg, South Africa): I have three questions. The first concerns the appearance of peristaltic failure in 38% of your Barrett's patients. How does that compare with the prevance of peristaltic failure in gastroesophageal reflux without Barrett's?

Arising from that, therefore, is this the cause or the result, and therefore, in the patients who have undergone operative corrections, is there any evidence of recovery of peristalsis or esophageal body dismotility after correction?

Second, is the old question about the prevalence of adenocarcinoma in Barrett's. There seems to be a difference in the incidence. In patients under surveillance for Barrett's, a low incidence of carcinoma develops. The other side of the coin is that most of patients, or a large proportion of patients, with adenocarcinoma of the esophagus have an underlying Barrett's. My question is, of these patients who presented with adenocarcinoma, how many of them presented with features of malignancy and how many of them were under surveillance and possibly under medical treatment for Barrett's either by yourself or another physician?

The third question is in terms of the operative tactics for malignant patients. In the light of zero incidence of malignant nodes along the splenic artery, will this lead you to any change in your tactics? In other words, would you leave out the splenectomy in the future in light of the findings of this series?

DR. FLETCHER MILLER (St. Paul, Minnesota): Your lab is so adequately set up to follow this that I think it will be very important in the future, and perhaps you have it even today, to present to us what are the actual follow-up data on the patients on whom you have performed the conventional operation for Barrett's. There might be other reports in the literature that do not get adequate results. It may be very important with the high incidence of cancer in these patients that a more radical approach is taken at the initial procedure.

DR. G. ROBERT MASON (Irvine, California): In his conclusions Dr. De Meester mentions that an esophagectomy alone is sufficient for intramucosal lesions.

In our experience we have been dreadfully disappointed in staging on a preoperative basis, and I would assume that when Dr. DeMeester does his resection he does the lymph node dissection first and then the esophagectomy and does not do the esophagectomy first but stages the lesion.

I wonder if he has found some way of staging these lesions that we do not know about.

DR. PAUL JORDAN (Houston, Texas): Dr. DeMeester, in this patient with dysplasia on whom you operated and found an incidental cancer, what made you operate on that patient and how do you decide when you operate for dysplasia?

THOMAS R. DEMEESTER (Closing discussion) Dr. Skinner commented on the need for surveillance, and we certainly would concur because we now believe that with adequate surgery, early disease can be cured. He also questioned about our experience with resection for high-grade dysplasia. We have operated on two patients with high-grade dysplasia and are following one after having an antireflux repair. In only one of the two operated on was an intramucosal carcinoma found. No cancer has been found during a 4-year surveillance period in the patient who had an antireflux repair.

Dr. Ellis raised the issue about prevalence and incidence. His incidence of malignant disease was 27%, which is very similar to ours. About a third of the patients we see with Barrett's esophagus present with malignancy.

He also asked about the incidence of malignancy degeneration and the expected data in this area. The study by Hameeteman et al. (*Gastroenterology* 1989; 96:1249–1256) indicates that it occurs in 1 of 50 patient years of follow-up. To put that in perspective, if you had 100 patients you were following with Barrett's esophagus, you should discover two cancers a year, or if you had 100,000 patients with Barrett's esophagus, you would expect to see 2000 cancers a year. This is about four times the incidence of cancer as you would expect to see in 100,000 individuals who had smoked one pack of cigarettes per day for 20 years. I would conclude that patients with Barrett's esophagus definitely merit surveillance. It is a very strong indicator of possible malignancy.

Dr. Ellis also went into a discussion about the extent of operation and so forth. I just want to re-emphasize what I said at the close of the presentation that the extent of the operation should be tailored to the extent of disease present. In patients with intermucosal carcinoma, we have not seen lymph node metastasis and we wouldn't recommend at this point a need for a lymph node dissection. A transhiatal esophageal resection can be done in this situation.

On the other hand, of those patients who have intramucosal tumors, five of seven had lymph node metastasis. In these patients, I would certainly stress the importance of removing the lymph nodes *en bloc.* These patients have early disease and could be potentially cured with adequate surgery. As I noted, five of those patients are alive and doing well because the lymph node metastases were removed. We should not accept the concept that once node metastases are present, all hope for cure is gone. It is, of course, if the surgery is inadequate.

Dr. Grosfeld talked about *camphylobacter,* and indeed, *camphylobacter* is associated with gastritis. We think that gastritis has four causes: drugs, alcohol, *camphylobacter,* and duodenal gastric reflux. If gastritis is seen in someone who doesn't ingest alcohol or drugs, the chances of it being due to duodenal gastric reflux based on sophisticated gastric pH monitoring is about 80%. On the other hand, if *camphylobacter* is present on gastric biopsy, the incidence of duodenal gastric reflux decreases significantly but still can be present in association with *camphylobacter.*

Dr. Jordan asked when to operate on a patient who has high-grade dysplasia. At this time most of us working in the field would proceed with surgery in patients who have high-grade dysplasia, provided the finding is confirmed by at least two pathologists who are experienced in calling this lesion. It is a fairly formidable operation to undertake on the basis of one pathologist's opinion and a 50% chance of having invasive carcinoma. On the other hand, we feel more comfortable proceeding with surgery in patients who have intermucosal carcinoma because we have evidence that this lesion is malignant. We have done CEA staining of esophageal specimens in such patients and find that intermucosal carcinomas stain positive, but high-grade dysplasia does not. Consequently high-grade dysplasia is not a cancer at this point. The recommendation for surgery is only based on the assumption that it might be there.

Dr. Miller asked about the development of cancer in patients after standard antireflux operation. We have not had a cancer develop in such patients to date. One of our patients has severe dysplasia and is being followed because of his heart disease. He has not developed a carcinoma over 4 years, but neither has his severe dysplasia gone away. His stricture has regressed and his esophageal ulcers have healed, but dysplasia has not gone away. Now there may be a possibility that if a bile diversion is performed in a person with severe bile reflux gastritis, the esophageal dysplasia may regress. It may be that bile is the cocarcinogen in this problem, even when the only reflux occurring is physiologic.

Dr. Mark asked about reversibility of Barrett's. In our experience, this does not occur very often. I was recently impressed by the work in Europe by Felcete, who does a standard bile diversion procedure in patients with Barrett's esophagus and has a 20% incidence of reversal of the lesion, so it may be that bile is more of a culprit than we realize.

Dr. Myburgh asked about failure of peristaltic and valve function in patients other than Barrett's, that is, those with esophagitis or stricture. Our studies indicate that peristalsis doesn't deteriorate until patients develop a stricture or Barrett's. We find in ambulatory monitoring of patients with gastroesophageal reflux disease that the incidence of esophageal contractibility of less than 30 mm of mercury is statistically greater in patients with strictures and those with Barrett's esophagus. Patients with esophagitis are similar to normal. So it appears that esophageal body function does not begin to deteriorate in gastroesophageal reflux disease until a stricture or Barrett's esophagus is seen. Of interest is that we have not been able to reverse the damage once it has occurred. This should encourage early surgery in patients whose esophagitis does not immediately improve on medical therapy.

Dr. Myburgh also asked if we have limited the extent of our operation for cancer based on our findings. Now that the splenic artery nodes are not involved in patients with early lesions of the lower third of the esophagus, we would no longer recommend that the splenic artery and its associated nodes be resected. We would continue to do so for early cancer of the cardia. We have started with the idea that we would do an extensive operation and tailor it down when we had evidence that it was appropriate to do so.

Dr. Mason asked how one determines whether there is intermucosal carcinoma. Intermucosal carcinoma is a lesion picked up on biopsy in a patient with no visible mass on endoscopy. If a patient has a visible mass on endoscopy, then the patient has either an intramural or transmural tumor. Obviously endoscopic ultrasound will allow us to differentiate between an intramural and transmural tumor in the future.

There was one other point I wanted to make that had to do with Dr. Condon's comment 'that you can do the same operation using the transhiatal approach.' Dr. Condon how do you know that all the nodes are removed with that operation? Early disease can involve the nodes, as we have shown, and I know you can't do as good a node dissection by the transhiatal route as you can with our transthoracic *en bloc* technique. I think that we should not limit our operation for early disease until we are sure that we are not compromising the patient's chance for long-term cure.

Ionized Calcium, Parathormone, and Mortality in Critically Ill Surgical Patients

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A prospective study measured ionized calcium and parathormone sequentially at 48- to 72-hour intervals in 25 surgical intensive care unit patients. Twelve patients (48%) died at mean day 40 and median day 26. Levels of ionized calcium, parathormone, blood urea nitrogen, creatinine, albumin, magnesium, and phosphate for patients who lived were compared with levels for patients who died. The incidence of hypotension, renal failure (creatinine ≥ 3.0), and bacteremia, as well as the amount of red cell, crystalloid, and colloid administration for the two groups was compared. Hypotension, bacteremia, red cells, crystalloid, and colloid were no different. On days 1 and 2 ionized calcium levels were significantly lower and parathormone levels significantly higher in nonsurviving patients; this difference persisted through days 3 and 4. Blood urea nitrogen and creatinine levels increased early in nonsurviving patients but renal failure, which occurred in nine nonsurviving patients, did not develop until mean day 14, median day 18. The phosphate level was slightly higher but still within normal range in nonsurviving patients. By days 5 and 6 ionized calcium and parathormone levels were no different in nonsurviving patients, despite there being no improvement in renal function. Magnesium and albumin levels were no different between groups. Ionized calcium levels are lower and parathormone levels higher early in nonsurviving patients. This difference is not readily explained by associated clinical conditions, including renal dysfunction. Although etiology remains unclear, low ionized calcium and elevated parathormone are early predictors of mortality in critically ill surgical patients.

THE ASSOCIATION OF decreased serum total calcium (TC) and ionized calcium (IC) levels with critical illness is well documented.[1-11] Because calcium is important for many cellular activities (*e.g.*, electrical conduction, contractility, enzyme and hormone activity), reduced calcium concentration has been suggested to cause decreased cellular and organ performance, particularly cardiovascular dysfunction.[2,3,6,11,12]

Hypovolemic hypoperfusion, sepsis, hypomagnesemia, rhabdomyolysis, and renal failure, as well as albumin and red cell transfusions, are all associated with diminished IC but are difficult to consolidate into one pathogenic mechanism.[2,4,5,9,10,13,14] The frequent coexistence of extracellular conditions fostering hypocalcemia (elevated phosphate levels, citrate infusion, 'relative' hypoparathyroidism, albumin infusion) with diseases that permit calcium migration into cells (hemorrhagic hypoperfusion, sepsis, pancreatitis, muscle injury) accentuates this difficulty.[1,3,10,12,15-18]

The clinical significance of hypocalcemia also is difficult to assess. Patients with the conditions listed above have a significant mortality risk and the relationship of hypocalcemia and parathormone (PTH) response to this risk is controversial.[4,10] Similarly controversial is the benefit of calcium administration, especially when intracellular calcium levels may be increasing.[10,12,19-22]

Our interest in calcium and PTH in critical illness began with a study of hypercalcemia in patients documented to have had multiple previous episodes of hypocalcemia.[7,23] This study and several others have used one-time or retrospective measures of calcium and PTH and therefore do not describe the 'natural history' of these variables as they relate to clinical factors and prognosis. The purpose of the present investigation was to study IC and PTH sequentially in critically ill surgical patients. Prospective, sequential data would be expected to clarify relationships with clinical factors and illness severity.

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Materials and Methods

Patient Selection

All patients admitted to the Surgical Intensive Care Unit (SICU) in the Rhode Island Hospital during a 3-month period were considered for study. Twenty-five consecutive patients expected to require SICU management for more than 72 hours were selected regardless of admitting diagnosis or surgical interventions.

Ionized Calcium and Parathormone Measurements

Serum IC level was determined using the NOVA ion selective electrode (NOVA Biomedical, Newton, MA), whose normal range is 4.8 to 5.2 mg/dL and coefficient of variance is 0.7%. Parathormone level was determined using the PTH-MM mid molecule radioimmunoassay (INCSTAR, Stillwater, MN), whose normal range is 29 to 85 pmol/L, minimum detectable level is 10 pmol/L, and coefficient of variance is 9.5%. Samples were collected within 48 hours of admission and thereafter at 48- to 72-hour intervals until discharge from the SICU. Most of the data were collected during the first 10 SICU days and provide the measurements for the analysis of variance (ANOVA) matrix described below. Data collected after 10 days were too few to be used for this analysis but were combined with the first 10 days' data for analysis by t test.

Clinical Data

Clinical data recorded prospectively were age; sex; primary diagnosis by disease category (*e.g.*, gastrointestinal, trauma); surgery by category (*e.g.*, gastrointestinal, cardiovascular); episodes of hypotension (systolic blood pressure less than 90 mmHg) and bacteremia; red cell transfusion; intake of total parenteral nutrition (TPN); incidence of renal failure (creatinine ≥ 3.0 mg/dL); and serum magnesium (normal, 1.2 to 2.3 mg/dL), serum phosphate (normal, 2.7 to 4.5 mg/dL), albumin (normal, 3.4 to 4.8 g/dL), and TC (normal, 8.5 to 10.5 mg/dL) levels. Data collected retrospectively were daily crystalloid and colloid administration, urine output, antibiotics administered, serum blood urea nitrogen (BUN), and serum creatinine.

Data Analysis

For ANOVA data were organized using 48-hour groupings (*i.e.*, days 1 and 2, 3 and 4, 5 and 6, 9 and 10), which allowed potentially 8 data points per patient and 200 data points for each measured variable. Because not all of the data were collected each day, no variable was measured 200 times. For the data listed under results, the total number of data points available for ANOVA is given in the tables. For instance, of 200 potential creatinine determinations, 142 were available for analysis. Data for surviving patients compared with data for those who did not survive during this hospital admission were analyzed using ANOVA corrected for repeated measures with individual means compared using the Newman-Keuls method.[24] Linear regression analysis was used to correlate individual PTH and IC values in both patient groups. Data collected after 10 days were too few for ANOVA. To analyze all IC and PTH data gathered in the study, including that beyond the first 10 ICU days, a t test was used. Data are presented as mean plus or minus standard error. Data were considered significantly different when $p < 0.05$.

Results

Demographic Data

Twelve of the twenty-five patients (48%) died at mean day 40, median day 26 (range, 5 to 153 days). The mean age of surviving patients was lower, but not significantly different from that of patients who did not survive (48 ± 6 years compared with 62 ± 4 years; $p = 0.06$). The admitting diagnoses for the surviving patients were trauma (n = 10), gastrointestinal (n = 2), and genitourinary (n = 1); for nonsurviving patients trauma (n = 4), gastrointestinal (n = 5), cardiac (n = 2), and genitourinary (n = 1). The first operations for surviving patients were abdominal (n = 7), orthopedic (n = 5), and genitourinary (n = 1); for nonsurviving patients abdominal (n = 5), cardiac (n = 2), orthopedic (n = 2), genitourinary (n = 1), and neurologic (n = 1). No patient had pancreatitis.

The incidence of hypotension during the first 10 SICU days was no different between groups. There were no differences between groups in quantities of crystalloid, colloid, TPN, red cells, and antibiotics administered during the first 10 days. There was no difference in the incidence of bacteremia.

There was a difference in the incidence of renal failure (9 of 12 nonsurviving patients compared with 0 of 13 surviving patients), but this began on mean day 14 (median day 18). Urine output, serum BUN, serum creatinine, magnesium, phosphate, and albumin levels for the two groups are listed in Table 1. Urine output was significantly less on days 3 and 4 in nonsurviving patients. Serum BUN levels were significantly elevated throughout the study period in those who did not survive. Similarly serum creatinine levels were significantly elevated on days 1 through 4 and again on days 9 and 10 in the nonsurviving patients. Also included in Table 1 are data calculated after removing the values of the single patient who had established renal failure on arrival in the SICU (BUN, 150; creatinine, 9). Removing this single patient's values from the calcu-

TABLE 1. *Renal and Serum Chemistry Data*

Data	Days 1–2	Days 3–4	Days 5–6	Days 9–10
Urine (L/24 hr) (125 points)				
Lived	2.12 ± 0.31	3.25 ± 0.51	2.65 ± 0.31	2.68 ± 0.25
Died	1.31 ± 0.18	1.64 ± 0.29*	1.92 ± 0.30	2.44 ± 0.43
BUN (mg/dL) (142 points)				
Lived	16.1 ± 2.2	12.0 ± 1.8	9.6 ± 1.4	13.7 ± 2.2
Died	39.6 ± 11.3*	34.5 ± 8.6*	25.1 ± 3.6†	40.4 ± 6.2*
BUN—1 (mg/dL) (138 points)				
Died	23.6 ± 3.7*	26.6 ± 3.6*	25.1 ± 3.6*	28.8 ± 3.6*
Creatinine (mg/dL) (142 points)				
Lived	1.18 ± 0.05	1.06 ± 0.07	1.03 ± 0.06	0.89 ± 0.09
Died	2.63 ± 0.74*	2.21 ± 0.64†	1.44 ± 0.15	2.78 ± 0.77*
Creatinine—1 (mg/dL) (138 points)				
Died	1.56 ± 0.16*	1.59 ± 0.14*	1.44 ± 0.15*	1.6 ± 0.22*
Magnesium (mg/dL) (60 points)				
Lived	1.32 ± 0.11	1.13 ± 0.13	1.37 ± 0.03	1.62 ± 0.07
Died	1.18 ± 0.10	1.14 ± 0.13	1.36 ± 0.12	1.55 ± 0.15
Phosphate (mg/dL) (58 points)				
Lived	2.78 ± 0.58	2.2 ± 0.26	2.65 ± 1.05	3.02 ± 0.36
Died‡	4.0 ± 0.89	3.61 ± 0.57	3.86 ± 0.82	2.98 ± 0.51
Albumin (g/dL) (48 points)				
Lived	2.1 ± 0.18	2.34 ± 0.08	2.6 ± 0.0	2.1 ± 0.17
Died	2.19 ± 0.18	2.24 ± 0.13	2.2 ± 0.23	2.04 ± 0.16

* $p < 0.01$ compared with L.
† $p < 0.05$ compared with L.
‡ $p < 0.05$ for the entire 10 days, but no individual pairs were different.

lations lowers the mean BUN and creatinine levels for the nonsurviving patients; however the standard error is also diminished and the statistical difference between values for surviving and nonsurviving patients is still significant throughout the study at the $p < 0.01$ level. Magnesium, phosphate, and albumin levels were no different at each data point. However, for the entire study period, phosphate levels were elevated, although still within the normal range, in patients who died.

Total calcium, IC, and PTH data are listed in Table 2. Ionized calcium and PTH data are presented in Figures 1 and 2. Patients who died had significantly lower IC and significantly higher PTH levels during SICU days 1 through 4 compared with levels measured in those who lived. Total calcium levels were lower in nonsurviving patients on days 3 through 6. The mean plus or minus standard error values for IC and PTH levels using every available data point are presented in Table 3. No patient had symptoms of hypocalcemia (perioral numbness, tetany). Hypercalcemia or elevated PTH did not develop in any patient after the first 10 days of the study.

Linear regression analysis showed no significant correlation between IC and PTH levels in patients who lived. In patients who died, a significant correlation was present (Fig. 3).

Discussion

In 1883 Ringer described the importance of extracellular calcium for organ function, specifically contraction of the isolated frog heart.[25,26] Since then the physiologic functions of extracellular and intracellular calcium have been found to include nerve conduction, blood coagulation, maintenance of cell membrane integrity, and hormonal action.[1,25,27,28] The extracellular-to-intracellular concentration gradient for IC (1000 to 10,000:1) demands active processes to pump calcium out of the cytosol across the cellular membrane or to sequester calcium in intracellular organelles such as the sarcoplasmic reticulum and mitochondria.[27] Recognition that elevated cytosolic calcium is associated with cell death highlights the importance of these energy-dependent mechanisms.[22,29]

The physiologic importance of decreased serum IC levels in acute critical illness has been difficult to define, especially because accurate measurement of IC concentration is problematic and clinical parameters in acute illness

TABLE 2. *Calcium and Parathormone Data*

Data	Days 1–2	Days 3–4	Days 5–6	Days 9–10
Total Calcium (mg/dL) (104 points)				
Lived	6.98 ± 0.24	7.52 ± 0.17	8.0 ± 0.31	7.68 ± 0.38
Died	6.58 ± 0.22	6.58 ± 0.21†	6.76 ± 0.30†	7.68 ± 0.35
Ionized Calcium (mg/dL) (88 points)				
Lived	4.03 ± 0.16	4.25 ± 0.08‡	4.33 ± 0.08‡	4.52 ± 0.09‡
Died	3.45 ± 0.09†	3.91 ± 0.14†‡	4.16 ± 0.10‡	4.41 ± 0.18‡
Parathormone (pmol/L) (47 points)				
Lived	72.3 ± 8.7	77.0 ± 10.5	71.4 ± 25.4	64.1 ± 6.4
Died	181.9 ± 36.3†	150.4 ± 29.7*	108 ± 18.6	55.0 ± 40.0

* $p < 0.05$ compared with L.
† $p < 0.01$ compared with L.
‡ $p < 0.01$ compared with previous data point.

are markedly variable.[1,2,4,8,18,20,30] The present study demonstrates that ionized extracellular hypocalcemia is common in critically ill surgical patients and that two distinct patterns of calcium and PTH are apparent early in patients who live compared with those who do not.

Patients who survive have a decrease in IC level followed by gradual increase during their first 10 ICU days and no significant increase in PTH level above normal levels. Nonsurviving patients have lower IC levels, which increase to survivor levels by days 5 and 6, and an early, marked, linear increase in PTH levels, which decrease to survivor levels by days 5 and 6. These early IC and PTH differences between surviving and nonsurviving patients are statistically different when all IC and PTH data are compared, including data gathered after the first 10 ICU days.

The normal PTH levels in patients who live, and in those who die at days 5 and 6, might be considered an 'inadequate' response. Bovine PTH increases in a linear fashion after ethylenediamine tetra-acetic acid (EDTA)-induced hypocalcemia.[31] Ionized calcium usually is maintained within tight physiologic limits. Therefore normal PTH levels with this degree of hypocalcemia cannot be readily explained. In contrast the early PTH increase in nonsurviving patients is more than double the survivor level. The linear relationship between PTH and IC suggests a more normal response, but at an increased threshold.

Several clinical indicators of severity, including hypotension, crystalloid administration, and red cell transfusion, were no different between study groups. The difference in age between the two groups approached statistical significance but does not easily explain differences in IC and PTH levels.

PTH is metabolized by both kidney and liver.[32] Nonsurviving patients had a higher incidence of renal failure,

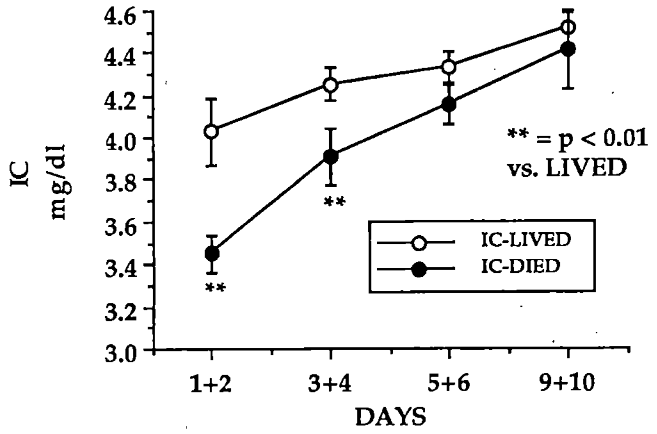

FIG. 1. Ionized calcium levels were significantly lower in nonsurviving patients than in surviving ones on days 1 and 2 and on days 3 and 4.

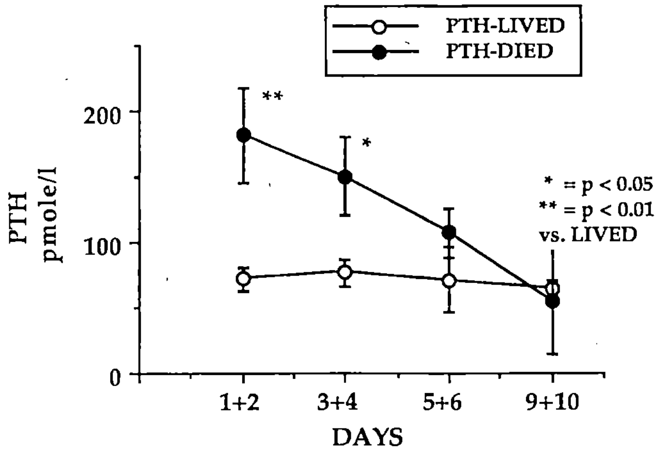

FIG. 2. Paratharmone levels were significantly higher in nonsurviving patients than in surviving patients on days 1 and 2 and on days 3 and 4.

TABLE 3. *All Calcium and Parathormone Data*

Group	Ionized Calcium mg/dL (data points)	Parathormone pmol/L (data points)
Lived	4.39 ± 0.03 (109)	78.1 ± 6.1 (97)
Died	4.15 ± 0.05 (90)	121.5 ± 7.9 (48)
p value	0.000	0.000

which may have impaired PTH breakdown. Phosphate levels were slightly higher in patients who died during the 10 days of the study. Because phosphate stimulates PTH secretion and is excreted by the kidneys, one could argue that all the PTH and calcium differences noted were secondary to early renal failure and that renal failure alone was the major determinant of death.

However the magnitude of renal failure as indicated by BUN and creatinine levels and by urine output changed little during the first 10 days. Furthermore phosphate and magnesium levels changed little, and phosphate levels remained in the normal range. Renal function was not dramatically improved on days 5 and 6, and yet IC and PTH levels in surviving and nonsurviving patients were no different at that time. If renal failure were the primary determinant of the alterations in calcium and PTH levels, these alterations would have been expected to continue as renal function did not improve or, in fact, worsened with approaching renal failure (creatinine ≥ 3 mg/dL), apparent by mean day 14. Renal failure and phosphate levels do not appear sufficient to explain the differences in calcium and PTH levels.

Citrate in transfused blood, increased phosphate concentration, renal failure, inadequate PTH concentration, fat saponification, albumin infusions, and deficient vitamin D action have been implicated as causes of decreased IC concentration in critical illness and can be classified as extracellular processes (chelation, binding to protein, decreased mobilization from bone, decreased intestinal absorption).[1,3,4,6,8,33] However because calcium appears to migrate into cells during many diseases (hypoperfusion, infection, pancreatitis, rhabdomyolysis), the measured decrease in serum calcium concentration may not represent a primary process in the extracellular space but rather failure of cellular mechanisms that maintain normal extracellular and intracellular concentrations.[1,2,5,12,13,15,17,34,35]

The cellular response to intracellular calcium accumulation may vary. A moderate increase in intracellular calcium might improve cell function just as digitalis or hypertonic saline improve cardiac muscle function.[26,36] The most severely injured cell, with diminished energy-dependent intracellular calcium regulation, would be expected to allow more accumulation. Intracellular calcium can activate protease and marked intracellular accumulation is toxic to cardiac and skeletal muscle, as well as to liver and kidney cells.[22,29,34,37] Parathormone may augment intracellular calcium migration directly (renal cells) or indirectly as calcium mobilization from bone increases the available extracellular pool.[27] Lower IC and higher PTH levels in nonsurviving patients who experienced renal failure are consistent with calcium-induced toxicity.

The controversial relationship between ionized hypocalcemia and mortality in previous reports is understandable given the low IC levels in surviving patients and the disappearance of differences by day 5. Previous studies may have sampled IC in patients at times when no difference would be recognized. Similar sampling issues may account for the normal PTH levels reported.[1,4,10]

More controversial still is the advisability of calcium administration in critical illness.[4–6,8,10,12,15,19,21] Calcium administration is beneficial when extracellular mechanisms for hypocalcemia predominate—citrate infusion, citrate elevation during liver transplant surgery, and hypoparathyroidism.[16,19,38,39] If calcium is migrating into cells, an exogenous increase in extracellular calcium might be detrimental because intracellular calcium can be toxic.[19,35]

Intracellular calcium migration and/or tissue deposition is accepted as the etiology of hypocalcemia during rhabdomyolysis. Symptomatic hypocalcemia is not seen.[14,35] Elevated PTH levels have been documented early in this disease. Calcium administration is not considered beneficial. In fact as muscle cells recover, hypercalcemia may develop, presumably secondary to extrusion of intracellular calcium or mobilization of tissue deposits. This hypercalcemia can result in pathologic calcium deposition

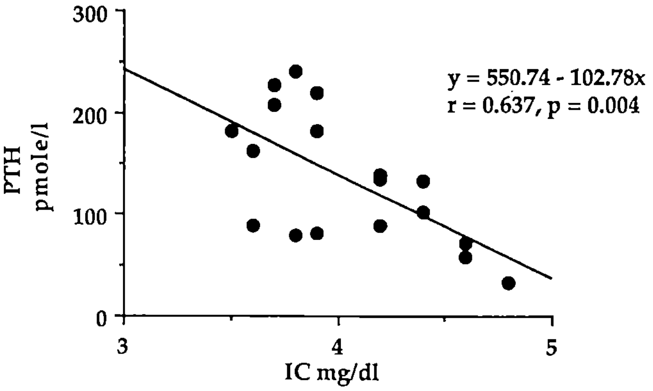

FIG. 3. This figure demonstrates the linear correlation between PTH and IC in patients who died.

and might be aggravated by early calcium therapy. During the hypercalcemic phase reported, PTH levels have ranged from nondetectable to elevated.[14,35,40] In one study elevated PTH was considered acute secondary hyperparathyroidism, similar to the pathophysiology proposed in our previous study of surgical patients.[7,14]

Hypercalcemia following hypocalcemia was not seen in the present study population. The previously estimated 15% incidence of hypercalcemia in critically ill surgical patients would have predicted three cases. Using rhabdomyolysis as an analogy, severe critical illness may be associated with intracellular calcium accumulation and resolution of disease with calcium extrusion. Hemorrhagic hypoperfusion, pancreatitis, and sepsis allow muscle uptake of calcium. Possibly intracellular accumulation followed by extrusion of intracellular calcium occurs to a lesser extent with these diseases than in rhabdomyolysis and has not been as clinically obvious. Because severity may be proportional to cellular calcium uptake, few patients may survive long enough to exhibit hypercalcemia.

No patient exhibited elevated PTH levels later in the hospital course. Therefore there was no documentation of the pathophysiologic sequence proposed in our previous study.

Decreased IC levels are common in critically ill surgical patients, regardless of underlying disease or surgical procedure. The nadir of IC concentration is early in the course of critical illness and is lower in patients who do not survive. Parathormone levels are markedly elevated early in patients who die but remain within normal limits in those who survive. Both extracellular and intracellular mechanisms influence serum IC concentrations in critical illness. If intracellular migration is the primary mechanism, then increased PTH concentration and administration of calcium may not be beneficial. Although etiology remains unclear, low IC and elevated PTH levels are early predictors of death in critically ill surgical patients.

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DISCUSSION

DR. CHARLES LUCAS (Detroit, Michigan): This important paper elucidates the sequential changes in the physiologic control of a vital ion, calcium, in critically ill patients. The authors have shown that the typical hypocalcemic response in critically ill patients leads to a rise in PTH. The correlation between reduced free calcium and the rise in PTH was significant in nonsurvivors. Our findings in septic and injured patients show that this correlation is significant in both survivors and nonsurvivors. This is true using both the amino- and carboxy-terminal assays.

This leads to my first question. Do the authors postulate an alternate pathway, possibly a prostaglandin, that blunts PTH release in their survivors?

The authors speculate as to whether the hypocalcemia results from the cellular influx of calcium from the ECF space. I doubt that this is the mechanism. The 10,000 to 1 ratio of extracellular to intracellular calcium permits a lethal influx of calcium without measurable changes in serum calcium. The magnitude of the ECF calcium change during a lethal cellular influx might be akin to the changes in wind velocity induced by passing gas in a wind storm.

The spectre of acute renal failure with hyperphosphatemia as a cause for increased PTH is raised. I agree with the authors that this is an unlikely mechanism. Our unpublished data on renal plasma flow, renal blood flow, inulin clearance, and creatinine clearance in hypocalcemic patients with elevated PTH show that this response occurs at all levels of renal perfusion and filtration independent of phosphorous levels. Let us not overlook a very important message in their patients. None of 13 of the survivors had renal failure, whereas 9 of the 12 nonsurvivors had renal failure. More importantly, during the critical days, 2 and 4 of the intensive care unit, the nonsurvivors, of whom 75% developed renal failure, excreted an average of 1.6 L of urine per day compared to the 3.25 L of urine per day in the survivors.

Our two senior residents here will carry that message back to their colleagues in Detroit so that we can continue the good message that keeping the kidneys healthy is the key to success in the intensive care unit.

The authors question the appropriateness of this PTH response, noting that similar calcium reductions in normal patients yield a higher PTH. Is there an altered threshold, they ask?

We must remember that we can only measure the serum levels of calcium assuming that the interstitial fluid calcium levels are identical. During the early period of illness in these patients, there are marked increases in the interstitial fluid volume and decreases in the interstitial fluid compliance. We cannot assume that the calcium level at the cell membrane and within the RER of the call, which has altered T tubules, is the same as the serum level.

Last the authors need to speculate for us as to how this, in my opinion, teleologic increase in PTH leads them to change or modify their recommendations of therapy in these critically ill patients. At a time when our cognitive friends are using all sorts of calcium channel blockers on the assumption that this will cause a reduction in intracellular calcium, at a time when we are afraid to add calcium therapy in hypocalcemic patients for fear of producing severe changes in the intracellular calcium levels, do the authors suggest that God wasn't looking when He caused this rise in PTH?

DR. EDWIN L. KAPLAN (Chicago, Illinois): Ionized calcium is decreased by citrate, it is decreased by heparin. Another thing that hasn't been mentioned is that it is related to acid base balance, and the authors present no data here.

For instance acidosis raises the ionized calcium and alkalosis lowers the ionized calcium. I am not certain that the authors looked for this.

I think the most important thing that they have shown is that the phosphate level is elevated on day 1 in their patients. I don't think this is some mystical thing that they are showing. I think that we have shown years ago that if you give 1 g of elemental phosphate, the serum phosphate level increases an hour or two later but it doesn't reach abnormal levels. Concomitant with this, the ionized calcium level falls and the PTH doubles. I think the level of phosphate that they have shown in my view may be sufficient to explain a great deal of the lowering of the ionized calcium and the rise of the phosphate. They have shown that this group had a higher creatinine level and a higher phosphate level. While it may not be statistically significant or outside of the normal range, I think it should not be discounted.

DR. JOHN BORDER (Buffalo, New York): I think we have another set of interesting observations here, but you need to put them together with other such observations.

In one of our studies it was clear that on the basis of one plasma analysis taken on an average of 9 days before death, we could predict with 98% accuracy who would die. Josef Fischer has a number of such studies related to amino acids, and I think that this is just one more of such studies. The interesting part about this is that these are all septic patients who, in past years, we would have said died of infection. I know of no way of predicting from bacteriologic data who will die, and in fact, when you take our bacteriologic data on such patients, those who have the most bacteriologic evidence of infection all survive. I think the problem with death in these patients is a metabolic problem. It is reflected in the amino acids and the ionized calcium that is reflected very much in the creatinine. That is sort of a sum total of protein catabolism, and that is what they die of. They are dying of metabolic exhaustion and we do not know how to treat it yet.

DR. ARLO CLARK (San Francisco, California): On initial reading I think we would all like to determine predictors of outcome, but I really wonder in this particular paper if the main factor is the patients' hypocalcemia. Although the PTH assay was a midregion PTH assay, it was probably not the best PTH assay because the new sandwich type assays are better.

Do the authors have any data on the patients before admission to the intensive care unit? The initial major differences were on the first day or the first few days in the intensive care unit. Presumably when the patients died, their calcium levels were the same as they were in the nonsurvivors.

I also wonder if they had any 1,25 vitamin D levels. Dr. Kaplan mentioned phosphate, which is certainly important.

I think renal function is especially important in this particular PTH assay, but the 1,25 vitamin D, perhaps the alpha hydroxylase effect may change early on in the course and influence calcium levels, which are then corrected by all the manipulations in the intensive care unit.

Perhaps the authors could speculate further on their hypothesis regarding the etiology of the mechanisms, because if we can define the abnormality, then perhaps we can correct it.

I also had some problem with their data. They said that 10 of the 12 patients who died were patients who subsequently developed renal failure, although there was just a slight increase in creatinine level initially. Yet 10 of 12 patients in their abstract did not have hypocalcemia initially in the first 4 days, and yet there are only 12 patients who were in that group of nonsurvivors. Perhaps it is sequentially that the differences occurred, but I would like them to answer that question.

DR. JOHN HOWARD (Toledo, Ohio): This group of patients is notorious for having a low serum albumin level. Would the authors comment on the roll of hypoalbumineminemia resulting in a low total serum calcium and thus a low ionized serum calcium level?

DR. KENNETH W. BURCHARD (Closing discussion): First to discuss the broad question of teleologic phenomena. I think the small amount of cellular migration is adaptive similar to the effect of the cardiac glycosides on cardiac muscle function, and what we may be seeing here is an exaggerated response that then becomes toxic. I liken it to the release of mediators locally, which are probably proper in the inflammatory response, and then when they are releasing in large quantities into the circulation they damage tissues, so a little bit is good. A lot is bad.

Is there another phenomenon affecting the parathyroid glands either locally or systemically? The parathyroid glands are not isolated from other influences such as the catecholamine response and other hormonal phenomena, the prostaglandins, and it may be that we are witnessing an altered threshold and that may be adaptive early also because the survivors did not increase their PTH level.

There have been many studies that have argued that the PTH response is inadequate and is responsible for the low ionized calcium, and it may be that it is proper to have this inadequate PTH response.

I did not analyze the pHs in these patients because we were measuring ionized calcium. Total calcium followed pretty well with the ionized calcium. Ionized calcium demonstrated some early differences that total calcium did not, so having measured ionized calcium should eliminate the need to measure pH.

The phosphate levels did not change throughout the first 10 days. Even though they were higher than the values in the survivors, phosphate did not diminish toward normal at the time we were seeing ionized calcium and PTH return to the survivor levels, so I cannot explain all the changes based on phosphate.

Calcium in excess in the cells activates protein kinases, which may then result in cellular injuries.

One of the questions I don't think we have answered is why was the death so much later than these pathologic changes. You would expect that if intracellular calcium accumulation is the major toxin that death would have occurred shortly thereafter. All we can say is that possibly this sets the stage for further insults to be more damaging later.

We measured serum albumin levels. They were no different in the two groups. We do not have any data before ICU admission, and we did not measure vitamin D levels.

The disease that has best demonstrated altered vitamin D levels with hypocalcemia has been rhabdoryolysis, which produces a profound increase in phosphate, severe, acute oliguric renal failure and reduction in vitamin D, which has been attributed to the renal failure in that disease.

Because we did not see severe renal failure early, we would not have expected to have major disruptions in the vitamin D production.

Surgical Aspects of Sclerosing Cholangitis

Results in 178 Patients

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Of 178 patients with sclerosing cholangitis treated since 1950, 88 patients had associated inflammatory bowel disease, 72 had no such history, and 18 had iatrogenic injury or stone disease. A total of 233 biliary operations were performed, with a 75% rate of temporary improvement after initial operation. Subsequent operations resulted in a lower success rate and a higher mortality rate. Radiologic findings included predominant extrahepatic, intrahepatic, and diffuse disease in 29%, 28%, and 43% of patients, respectively; no survival differences were noted. Seventy-five of one hundred three deaths (73%) were related to liver failure, bleeding, or sepsis. Of 14 patients undergoing portosystemic shunt, 13 died of surgical complications or related disease. Orthotopic liver transplantation was performed in 16 patients and resulted in eight deaths, mainly in patients who had previously undergone extensive surgical treatment. No survival differences were seen between the patients with inflammatory bowel disease, those without the condition, or those who had colectomy. Surgical treatment in patients with sclerosing cholangitis should be minimized. Orthotopic liver transplantation should be offered as the treatment of choice for patients with portal hypertension, refractory cholangitis, advanced cirrhosis, or progressive liver failure.

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SCLEROSING CHOLANGITIS IS an insidious and uncommon inflammatory disease affecting the biliary ductal system that leads to obliteration and fibrosis of the ducts and, ultimately, to biliary cirrhosis. Inflammatory bowel disease (IBD) is associated with most cases of primary sclerosing cholangitis.[1] However other conditions, such as recurrent biliary infections, acquired immunodeficiency syndrome,[2] previous biliary tract surgery, bile duct anomalies, or stone disease, can result in similar lesions and clinical profiles. A significant number of patients have no demonstrable underlying cause. A high index of suspicion clinically combined with biochemical and histologic abnormalities may suggest sclerosing cholangitis;[3] however the presence of specific radiologic abnormalities[4] confirms the diagnosis. Several medical therapies have been suggested for the treatment of patients with sclerosing cholangitis, with little success reported.[5–7] Multiple surgical approaches for the relief of obstruction or cholangitis have been described, but as the number of procedures has increased, less than satisfactory results have been reported.[7–9] Liver transplantation has emerged as the treatment of choice when portal hypertension complicates the patient's course.[10,11] In this report we describe our experience with 178 patients who have undergone treatment for sclerosing cholangitis at the Lahey Clinic Medical Center since 1950.

Patients and Methods

A computerized record system was used to identify 178 patients with sclerosing cholangitis seen between 1950 and 1989. The diagnosis was based on clinical, biochemical, and histologic parameters combined with essential radiologic findings of stricture and dilatation of the biliary tree. Vital statistics such as the patient's age when symptoms first occurred, the initial presenting symptoms, and the age at death were recorded.

Symptoms and signs of sclerosing cholangitis (Table 1) included jaundice, pruritus, acholic stools, and cholangitis (fever, chills, and abdominal pain). Portal hypertension

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TABLE 1. *Symptoms and Signs of Sclerosing Cholangitis*

	Primary Sclerosing Cholangitis		Sclerosing Cholangitis
Sign	nonIBD (% of Patients)	IBD	Others (% of Patients)
Jaundice	76	57	89
Fever	77	55	67
Chills	79	69	89
Acholic stools	86	77	94
Abdominal pain	100	84	89
Cholangitis	69	55	89
Ascites	26	32	5
Varices	25	30	17
Encephalopathy	28	32	17
Cirrhosis	40	50	11

nonIBD, no history of inflammatory bowel disease. IBD, inflammatory bowel disease. Others, iatrogenic injury or stone disease.

was suggested by the presence of ascites, encephalopathy, edema, or documented esophageal or gastric varices. A subgroup of 28 asymptomatic patients was recognized by biochemical abnormalities alone, which prompted cholangiography and the subsequent diagnosis of sclerosing cholangitis.

Abnormal results were found on biochemical tests, which included the standard battery of liver function analyses: bilirubin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase, albumin, and coagulation profiles such as prothrombin time and partial thromboplastin time.

Findings of cholangiographic studies were reviewed in all but three patients by one radiologist (FJS) from reports in the records of patients seen before 1978 or films available since that time. These included endoscopic retrograde cholangiopancreatograms (ERCP) in 56 patients and operative cholangiograms in 91 patients, T tube in 22 patients, transhepatic in 5 patients, and intravenous in 1 patient. The predominant sites of involvement were divided into extrahepatic (including bifurcation), intrahepatic, and diffuse intrahepatic/extrahepatic areas.

Pathology reports were available for review in all but 19 patients from liver or bile duct biopsies or from native hepatectomy specimens in those patients undergoing transplantation. Findings consistent with sclerosing cholangitis included pericholangitis, thickened ducts, hyperplasia, and ductal proliferation combined with varying degrees of fibrosis or frank cirrhosis.

Primary sclerosing cholangitis was associated with the presence of coexisting IBD in 88 patients and was confirmed by clinical history, barium studies, and by colonoscopy and biopsy in 33 more recently treated patients. Chronic ulcerative colitis and Crohn's disease were distinguished on the basis of classic radiologic findings or biopsy. When these findings were not typical, the patients were classified as having indeterminate colitis. Types of involvement included pancolitis, left-sided colitis, and small bowel disease. In addition 39 patients who underwent colectomy were assessed for the influence and timing of this procedure on the outcome of treatment for sclerosing cholangitis.

Seventy-two patients with characteristic clinical, biochemical, and cholangiographic findings of primary sclerosing cholangitis were identified who had no history or evidence of inflammatory bowel disease (nonIBD). Another 18 patients (Others) with either well-documented injury to the bile ducts (12 patients) or long-standing recurrent biliary tract stone disease (6 patients) were analyzed as a separate group. The clinical and radiologic characteristics of these patients were indistinguishable from those of sclerosing cholangitis.

The indications for operation, operative reports, and outcomes were evaluated for all patients undergoing surgical intervention, which included 233 biliary procedures, 39 colectomies, 15 portosystemic shunts, 16 orthotopic liver transplantations, and 19 miscellaneous procedures. The cause of death was documented in all patients not lost to follow-up. The development of bile duct or colon cancer was considered separately and compared between nonIBD and IBD patients. Survival distribution was analyzed using the BMDP1L Kaplan-Meier product-limit method on patients with primary sclerosing cholangitis. Statistical significance of differences between distributions was analyzed according to the BMDP1L log-rank method (Figs. 1 and 2). Univariate survival effects of variables such as the presence of IBD, the effect of colectomy, and the extent of radiologic involvement showed no significant difference on log-rank analysis of stratified Kaplan-Meier distributions. Lack of statistical significance (NS) was defined as two-tailed $p > 0.05$.

Follow-up information was obtained for 151 patients from direct patient contact, referring physicians, or death certificates. Twenty-seven patients were lost to follow-up at a median of 7.5 years (range, 10.2 months to 20 years).

Results

The nonIBD and IBD groups were predominantly male (98 of 178 patients and 43 of 72 patients, respectively) compared with patients in the Others group (8 of 18 were male). The median age at onset of primary sclerosing cholangitis was 41.6 years (range, 14.9 to 74.5 years) and 46.8 years (range, 28.5 to 77.1 years) in the Others group. Clinical signs and symptoms were similar in all groups, with jaundice, cholangitis, and abdominal pain noted in most patients (Table 1). Complications of portal hypertension and the development of cirrhosis were more frequent in patients with primary sclerosing cholangitis

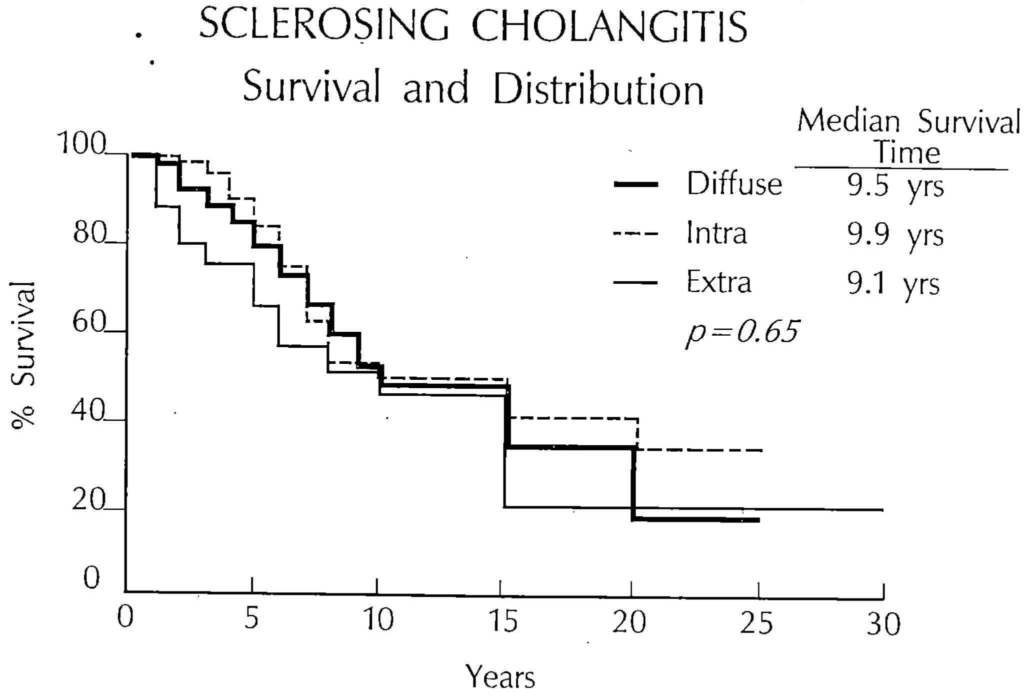

FIG. 1. Patient survival and distribution of sclerosing cholangitis. Significance of differences of distribution was analyzed by the Mantel-Cox log-rank test.

compared with those in the Others group who frequently presented with cholangitis. The bilirubin and alkaline phosphatase levels at diagnosis were elevated in almost all patients.

Surgical treatment included 233 biliary tract operations, 15 portosystemic shunts, 16 orthotopic liver transplantations, 39 colectomies, and 19 unrelated abdominal procedures. The results of the specific biliary tract operations are listed in Table 2. Cholecystectomy and common duct exploration and or dilatation were the initial operative procedures, with jaundice or cholangitis the most common indications. Most patients improved initially and few died. Subsequent surgical procedures included bilioenteric anastomoses, duct dilatation, or insertion of

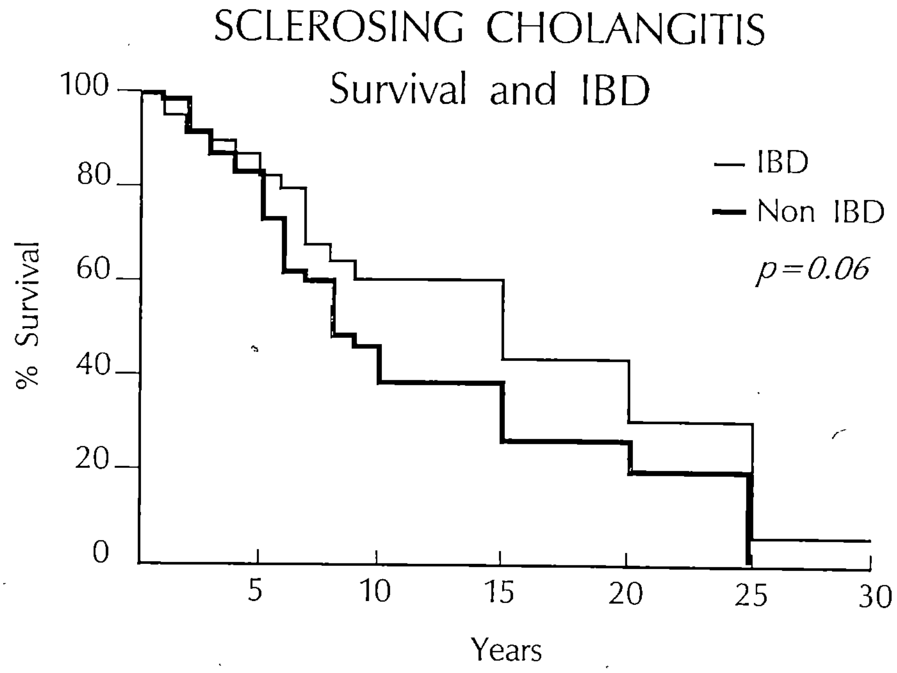

FIG. 2. Survival in patients with sclerosing cholangitis with and without inflammatory bowel disease. Significance of differences of distribution was analyzed by the Mantel-Cox log-rank test.

TABLE 2. *Types and Short-term Results of 233 Biliary Tract Operations*

	No. of Initial Operations		No. of Subsequent Operations	
	PSC	Others	PSC	Others
Cholecystectomy	32	15	—	—
Duct exploration/dilatation	18	3	52	23
Bilioenteric anastomosis	5	—	36	13
Transhepatic stent	11	—	17	8
Short-term results				
Improved	75%	67%	41%	39%
Unchanged	24%	30%	47%	46%
Died	1%	3%	12%	15%

PSC, primary sclerosing cholangitis. Others, iatrogenic injury or stone disease.

transhepatic stents and were associated with less success and more deaths. Fifteen portosystemic shunts were performed in 14 patients, with 13 deaths. Four of these patients died after operation, 3 from recurrent variceal bleeding in 1.5 years, 3 from bleeding during orthotopic liver transplantation up to 4 years later, and 3 from liver failure 1 to 3 years after operation. The cause of death therefore was liver related in all patients.

The overall mortality rate was 58% and appeared to be the highest in the nonIBD group (71%). The median time from diagnosis until death was 10.4 years (range, 1 month to 28 years). Liver failure or sepsis was responsible for more than 50% of the deaths and variceal or postoperative bleeding caused 19% of the deaths. Bile duct cancer was found in 11 patients with primary sclerosing cholangitis (7 nonIBD and 4 IBD) and in no patients in the Others group. Colon cancer was seen in 3 patients with primary sclerosing cholangitis and in no patients in the Others group. Rapid deterioration of otherwise stable disease was noted in 8 patients during a median of 9.4 months (range, 40 days to 15 months).

Radiologic evidence of predominant intrahepatic disease (Table 3) was seen in 49 patients (16 nonIBD, 30 IBD, and 3 Others). These patients underwent a total of 83 operations, with a median survival time of 9.9 years. Diffuse intrahepatic and extrahepatic disease was seen in 76 patients (35 nonIBD, 35 IBD, and 6 Others) who underwent a total of 146 operations, with a median survival time of 9.5 years. Fifty patients with extrahepatic disease only (19 nonIBD, 22 IBD, and 9 Others) underwent 14 anastomoses and 24 dilatations and stentings. Of these patients, 12 died of liver-related causes. The median group survival time was 9.1 years. Survival time therefore was not significantly different among patients with extrahepatic, intrahepatic, or diffuse disease (p = 0.65; Fig. 1).

Well-documented IBD was noted in 88 patients. Chronic ulcerative colitis, Crohn's disease, and indeterminate colitis were seen in 70, 15, and 3 patients, respectively. Pancolitis was noted in all 3 patients with indeterminate colitis compared with 60 patients (86%) with chronic ulcerative colitis and 9 (60%) with Crohn's disease. The median duration of IBD was 10.1 years (range, 1 month to 33 years). Differences of 5-year survival rate between patients with IBD and other patients with primary sclerosing cholangitis (Fig. 2) approached significance, with 5-year survival rates of 82.8% and 73.6%, respectively (p = 0.06, BMDP1L log-rank). Colectomy was performed in 39 patients for management of severe colitis, except for six asymptomatic patients with rapidly worsening primary sclerosing cholangitis. Of these 6 patients, 4 died of liver-related complications, 1 underwent orthotopic liver transplantation and was doing well at 1.5 years, and 1 had stable disease at 5.6 years follow-up. In 14 patients, colectomy was performed a median of 29.4 months before the diagnosis of primary sclerosing cholangitis (range, 1 month to 15 years) and in 21 patients a median of 7.1 months after the diagnosis (range, 1 month to 14.5 years). Primary sclerosing cholangitis was diagnosed in four patients at the time of colectomy. Symptomatic stomal varices developed in 10 patients, which required local surgical management in 7 patients and included reimplantation of stoma (2 patients) or simple oversewing (5 patients). These procedures failed in all patients. Portosystemic shunt subsequently was performed, which was fatal in all patients. The causes of death included liver failure in five patients and variceal bleeding in one. Another patient died during orthotopic liver transplantation of uncontrollable hemorrhage. The survival of patients who had colectomy was not significantly different when compared with that of other patients with IBD or those with primary sclerosing cholangitis (p = 0.16).

The median survival time of patients whose liver biopsies showed fibrosis was 9.4 years (range, 1 to 23 years). For those with the diagnosis of cirrhosis, the median survival time was 4.8 years (range, 4 months to 11 years).

Orthotopic liver transplantation was performed in 16 patients and abandoned in one who was found unexpectedly to have extensive bile duct cancer. The median age at transplantation was 37 years (range, 26 to 62 years) and there was a predominance of women (10 women and 6 men). Inflammatory bowel disease was noted in 10 patients: chronic ulcerative colitis in 8 patients and Crohn's

TABLE 3. *Biliary Tract Disease Distribution and Survival*

	Extrahepatic	Intrahepatic	Diffuse
No. of patients	50	49	76
No. of operations	54	83	146
No. of deaths	28	29	46
Median survival (years)	9.1	9.9	9.5

disease in 2. Twelve patients had undergone previous operations, including biliary tract procedures (n = 8), portosystemic shunts (n = 4), or colectomy (n = 3). Six of eight deaths due to orthotopic liver transplantation were in these patients. Three deaths were caused by massive intraoperative hemorrhage.

Abnormal results on liver function tests prompted radiologic evaluation in 28 asymptomatic patients (5 nonIBD, 23 IBD), with a median follow-up of 10.3 years. Surgical intervention was performed in 18 patients and included colectomy in 13 patients (8 of the 13 had colectomy only), portocaval shunt in 1 patient, and 21 biliary tract procedures in 9 patients. Four patients died: one of liver failure, one of variceal bleeding, and two of heart disease.

Of 47 current survivors, 18 patients remain asymptomatic, 16 remain stable despite abnormal findings on laboratory tests and cholangiograms, and 13 have had progression of disease and are being considered for liver transplantation.

Discussion

This large series allows the evaluation of the management of sclerosing cholangitis over many years. The treatment used has been as varied as the many proposed and yet unknown causes of the disease. The clinical course of sclerosing cholangitis may be indolent for years, with inexorable progression, or can be swift. In either case the ultimate development of complications demands treatment.

The goal of initial treatment is the palliation of cholangitis and obstructive jaundice at an acceptable risk for the patient that permits a reasonably good quality of life. The results in our patients who have had differing distributions of disease indicate that the survival time in patients with diffuse disease is the same as that in patients with extrahepatic disease only, a situation in which relief of obstruction is thought to be mechanically possible.[9] However, in our experience, duct exploration with dilatation and cholecystectomy gives only temporary favorable results in most patients (Table 2). Such treatment can be performed with low risk. With subsequent operative procedures, including operative dilatation, stenting, and anastomosis, the risk increases and the proportion of satisfactory results declines to less than one half.

The role of liver transplantation in the management of sclerosing cholangitis has emerged as a viable choice for these patients. The overall survival rate reported for all adult patients undergoing orthotopic liver transplantation is 75% to 80% at 1 and 2 years.[10] Survival for patients with primary sclerosing cholangitis falls short of this. The Pittsburgh group[11] reported 1- and 2-year actuarial survival rates of 71% and 57%, respectively, after orthotopic liver transplantation and related increased morbidity and mortality rates to previous surgical treatment. It should be noted that 9 of the 18 deaths in this series were due to technical problems associated with the procedures performed before July 1986. Previous biliary tract surgery, portosystemic shunts, and colectomy in a patient with portal hypertension make access to the liver during transplantation difficult and at times impossible. Indeed in our series six of eight deaths in the orthotopic liver transplantation group occurred in patients who had multiple previous operations. It is reasonable to assume that the survival rate for orthotopic liver transplantation in patients with sclerosing cholangitis would approach that for liver transplantation for other indications if the procedure was performed earlier in the course of the disease and in patients who had undergone only one biliary tract procedure without portosystemic shunt or hilar anastomosis.

Percutaneous transhepatic biliary dilatation or occasionally retrograde endoscopic dilatation offer possible solutions to this problem, especially if an anastomosis has been performed earlier in the patient's course and has become subsequently narrowed. Thus, if a patient has undergone initial operative dilatation or anastomosis, has a recurrence of jaundice, and is faced with undergoing a less-than-optimal second operative procedure, percutaneous manipulation would be the preferred treatment before resorting to liver transplantation. Previous reports[12,13] on the usefulness of these techniques have indicated that the results do not equal those for traumatic strictures but that the success rate is sufficient for a trial.

Patients with portal hypertension in whom variceal bleeding, ascites, or encephalopathy develops should undergo orthotopic liver transplantation as an initial procedure. In the past portosystemic shunt was considered in the good-risk patient who presented with variceal bleeding in an attempt to 'buy time' before the need for transplantation. The many complications that occurred after shunt surgery combined with the less-than-optimal results after liver transplantation associated with previous biliary tract surgery have persuaded us to proceed with orthotopic liver transplantation rather than shunt surgery. The main consideration is the avoidance of operation around the liver hilum. If shunts are considered, a distal splenorenal shunt is preferable to a central one. A Sugiura procedure[14] is another alternative.

If a method of prognosticating the course of any given patient were available, one could choose logically between early transplantation and delayed drainage tactics. Wiesner et al.[15] have attempted this through a statistical survival analysis that they characterize as a major first step but not one with great reliability. Cameron et al.[9] have suggested that in patients with rising serum bilirubin values who have had previous intubation, biliary operations, or both, liver biopsy should be performed because the presence of cirrhosis should prompt the serious consideration of transplantation. Our experience with needle biopsy of the liver leads us to suspect its accuracy and ability to prognosticate. However in this series the prognosis in patients with cirrhosis on open liver biopsy (53 cases with 27 deaths) was 4.8 years survival (range, 4 months to 11 years) compared with 9.4 years (range, 1 to 23 years) with a diagnosis of fibrosis (34 cases with 18 deaths).

As has been found by others,[7,16] colectomy for the treatment of sclerosing cholangitis in patients with IBD has no value. Furthermore it may be followed by the development of stomal varices, a particularly difficult complication. In addition the presence of a stoma can impede exposure for transplantation.

The occurrence of bile duct cancer in this series was 6.2% (11 of 178 patients), which supports the occurrence reported in another series.[7] Sudden deterioration in an otherwise stable patient should be viewed with concern. Routine brushings and cytologic analysis of percutaneous or endoscopic biopsy specimens should be performed. In the patient undergoing orthotopic liver transplantation, distal recipient bile duct sections should be examined by frozen section to avoid unexpected findings at operation.

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DISCUSSION

DR. HENRY PITT (Baltimore, Maryland): I would like to thank Dr. Martin and her coauthors for the opportunity to review their manuscript and congratulate them on a report of one of the largest series of patients with sclerosing cholangitis.

This analysis is important because it provides data on the natural history of patients seen at one institution over 38 years. In many respects this report is similar to that recently published in *Hepatology* by Weasner and his Mayo Clinic colleagues. They followed 174 patients seen over 15 years and found a median survival rate of 11.9 years, which is similar to the 10.4 years observed in the Lahey Clinic Report.

The Mayo Clinic group emphasized that five factors were important in predicting survival. These factors were age, serum bilirubin, hemoglobin, the presence of inflammatory bowel disease, and the degree of fibrosis or cirrhosis on liver biopsy. These factors were then used to predict whether patients were at low, intermediate, or high risk.

You looked at inflammatory bowel disease and your data differ from those in the Mayo Clinic report. Do you have any information from your data on the effects of age, bilirubin, hemoglobin, or cirrhosis on outcome?

You have also analyzed the cholangiographic distribution of the disease and found no influence on outcome. One problem with this analysis is that your patients were managed in so many different ways over such a long period of time.

In addition you did not analyze separately those patients with primary involvement of their hepatic duct bifurcation. Do you have any data on outcome with respect to that subgroup?

Analysis of your surgical results is also difficult again because so many different procedures were performed over such a prolonged period of time. Nevertheless you have recommended avoidance of biliary tract surgery in favor of transplantation. This recommendation from your analysis is a little hard to understand because 50% of your patients undergoing transplantation did not survive that operation.

In the manuscript you also quote the Pittsburgh transplantation data and suggest that previous biliary tract involvement influences outcome of transplantation. To my knowledge the Pittsburgh data document that previous surgery makes the transplant more difficult but does not affect long-term survival.

As you know we have recommended resection of the hepatic duct bifurcation and long-term transhepatic stenting for patients with sclerosing cholangitis who have primary involvement of the extrahepatic duct with or without bifurcation involvement and no established cirrhosis.

We continue to perform this operation in carefully selected patients and believe that we actually help them. This slide documents the survival data of 31 of these carefully selected patients operated on at John Hopkins with a median follow-up of 5 years.

According to the Mayo Clinic model these are high-risk patients and should have had 5- and 8-year survival rates of approximately 20%, and 10%, respectively.

As you can see, with our procedure, the 5- and 8-year survival rates were 77% and 61%, respectively. Only three of these patients have required liver transplantation, which has been performed successfully in each case. We believe our procedure is helpful because it treats both extrahepatic and intrahepatic disease. My final question, therefore, is whether you have applied our approach to any of your noncirrhotic patients, and if so, with what results?

DR. CHRISTOPH BROELSCH (Chicago, Illinois): Sclerosing cholangitis has emerged as one of the most important indications for liver transplantation along with postnecrotic cirrhosis and primary biliary cirrhosis.

Before this was accepted, however, surgeons and radiologists struggled through the disease that presented itself with a variety of predominant symptoms and interdependent complications such as jaundice, cholangitis, pain, and chills.

The experience of the Lahey Clinic during a 40-year period portrays a dilemma. After diagnosis the disease can progress anywhere between months and 28 years. Surgical intervention remains an important intermediate treatment, in addition to the final treatment, which should be transplantation.

Retrospective analysis of 233 biliary tract operations deserves special consideration. Although it is historical rather than prospective, it exemplifies the problem of too many surgical procedures and too many different procedures being performed for too few long-term improvements. While initial operations yielded a 75% short-term improvement rate, subsequent operations arrived at improvements only of biliary drainage had more than a 50% failure rate.

At what time does a patient benefit most from surgery? I think an analogy to biliary atresia is appropriate here.

We learned to examine the liver disease itself and not simply to treat intermittent complications by various drainage procedures.

According to the radiologic findings, the authors differentiate between three types of sclerosing cholangitis. While it is conceivable that the diffuse and the enterohepatic types of sclerosing cholangitis are not amenable to surgical drainage procedures, the extrahepatic type and the type Dr. Pitt refers to as including involvement of the bifurcation, should have a different prognosis.

The data of the Lahey Clinic indicate that the radiologic classification is irrelevant for prognosis, and I think that the data are convincing that drainage *per se* has no effect on the progression of the disease provided there is no simple mechanical obstruction.

Various gastroenterology textbooks describe a form of segmental sclerosing cholangitis, an extrahepatic noncirrhotic type of sclerosing cholangitis, which we have seen in a few patients and in whom the liver involvement is minimal.

We regard the type described by Dr. Pitt as the correctable type of sclerosing cholangitis, similar to the correctable type of biliary atresia, in which hepatoenterostomy or percutaneous drainage is indicated.

The question I have for the authors is: have they also seen this specific type more frequently in the recent series? Do they think there is a practical reason for maintaining the classification into three types?

The second question is different from 40 years ago. The diagnosis and the type of sclerosing cholangitis is obtained by ERC today quite accurately and drainage procedures, including general stenting, ballooning, and nasobiliary stenting, have advanced substantially.

Has this changed the approach of the authors at the Lahey Clinic rather to abstain from surgery and primarily exhaust the endoscopic procedures first?

Less surgery is generally advocated because it complicates transplantation.

Transplantation can be performed relatively safely with a high success rate and you can see that about 80% of the sclerosing cholangitis patients in this series of 67 survived.

The complicating factor in these patients, I believe, was not just adhesions or portal hypertension from previous surgery but also adhesions and infection from cholangitis or inadequately drained percutaneous devices such as percutaneous drainage in the presence of cirrhosis.

I would suggest avoiding any external drainage and I would like to ask the question whether, in your transplant series, you can identify percutaneous drainage as being more of a complicating factor than just a previous surgery.

The Pittsburgh group reported a series of 56 patients 2 years age, and they have not addressed in their review the question of recurrence of the disease.

Have you seen any recurrence of the sclerosing cholangitis in your series of 8 patients? We have not seen this in our series of 7 patients, but as we know particularly from data from Europe, there is a potential for recurrence in primary biliary cirrhosis, as identified by antiomitochondrial, antinuclear antibodies and these display similar potential for recurrence in sclerosing cholangitis.

DR. CARLOS PELLEGRINI (San Francisco, California): I would like to make a comment regarding the philosophy of the paper. When you have such a large number of patients and such a prolonged follow-up, there are some conclusions that can be made that will be valid. However, when you showed that extrahepatic disease and intrahepatic disease eventually have the same long-term survival rate, there is potential for confusion. When you lump patient groups like this it becomes very difficult, at least from reading the abstract, to understand what is the final conclusion of this paper.

When one evaluates cirrhotic patients who developed portal hypertension, the mortality rate for that particular group undergoing any kind of biliary tract surgery will be six or seven times that of the correction of a simplar biliary stenosis. I wonder if the authors in the closing remarks can give some specific guidelines for specific groups of patients. For example, what is the treatment of choice now for someone who presents with a segmental obstruction of the extrahepatic biliary tract? Is that a patient who should be subjected to transplantation, for example?

I think that most people agree that end-stage liver disease is an indication for transplantation, but is the message of this paper that transplantation should be performed to avoid some of the complications that are seen?

Along the lines of what Dr. Braasch brought up, the interventional radiologic procedures, dilatation, placement of catheters in the bile duct, and internal drainage increased the risk in these patients of developing further problems and not their being candidates for transplantation. It is important if you have such a large series to divide and allocate the patients to different groups.

DR. WILLIAM P. LONGMIRE, JR. (Los Angeles, California): I just rise to ask if the authors have had any experience with the development of cancer in their patients. About 35 years ago before this Association, Bill Altemeier presented a paper in which he and his pathologists clearly distinguished between the cancer of the bile duct and sclerosing cholangitis.

Most biliary tract surgeons in the intervening years have felt that they could differentiate these two lesions primarily on the basis of the x-ray examination. I know definitely in our series and some of our long-term follow-ups we have seen patients who undoubtedly started with sclerosing cholangitis and over a period of years developed cancer of the bile ducts.

This is particularly important in some of these long-term cases in which transplantation is a possibility. Our transplantation experts tell me that they have the problem of seeing these patients who have been followed to the point where they have developed cancer in their bile ducts and they have not been able to do a successful transplant.

I wonder if in the Lahey series, with this long-term follow-up, was there the development of cancer in their patients?

PROFESSOR HENRI BISMUTH (Villejuif, France): In our center, in the group of patients referred for transplantation for sclerosing cholangitis, we found cancer in 20% at the time of transplantation. In one half of them there was extrahepatic spread and liver transplantation was not indicated. In one half of them the cancer was found in the specimen of the liver transplantation.

In addition, considering the past history of these patients with cancer, we were not able to find any sign proving the presence of cancer, even just before transplantation. Is there some special investigation to detect the cancer in these patients before considering conservative treatment?

DR. F. M. MARTIN (Closing discussion): The first thing I would like to say is that sclerosing cholangitis is indeed a pernicious disease. Even though it is a benign disease, it takes an indolently malignant course. It is a progressive disease and it seems to me that regardless of what you do during the course of that disease, it is progressive. About 50% of these patients develop cirrhosis and liver-related complications.

Dr. Pitt commented on the Mayo Clinic study, and when you actually look at the Mayo Clinic series and compare it to our series, there are many similaries. The numbers are similar. The age group ranges are similar. But when you look at the patients, they quote 6 years. Our follow-up is 10.3 years, during which time 34% of their patients died, and 58% of our patients died, and I suspect that when they follow them out to 10 or 11 years their number of patients who die will increase as well.

The effects of age and bilirubin and a very elegant manipulation of these data from the Mayo clinic have showed a low risk and a high risk, and intuitively we, as surgeons, can identify those patients. The intermediate-risk group is the one that is least definable and that is the one that seems to have this sort of progressive, slowly stable course, and during that time of their disease, evaluating these parameters at any given time is very difficult for me because bouts of cholangitis or bouts of obstruction will change those symptoms. These patients will improve with surgical or nonsurgical manipulation, but overall they progress. So I am not convinced that we can add this model to the entire series.

The important group to concentrate on is the asymptomatic group in our series because these were people who we could actually follow over time who had no cirrhosis to begin with. In that group 4 patients died and 14 patients developed progressive disease, so that clearly confirms this progression of disease.

Dr. Pellegrini comments about the segmental distribution and when to do liver transplants, I will try to answer all at once. As a member of the Pittsburgh group right now, I am increasingly impressed with the number of patients with sclerosing cholangitis who are referred to us, having been turned down at other centers. The reason they are turned down at other centers is because of multiple and previous surgeries. Some of the patients have portal vein thromboses that are complications of various shunt procedures, and many are very, very high risk. In Pittsburgh we transplant these patients and we suffer with these patients. Patients who are referred to transplant centers should be referred early. The initial approach to patients with either cholangitis or segmental disease should probably be nonoperative. The radiologists have presented some very nice data suggesting that there is a 50% or 60% improvement in patients who have bile duct dilation. That is probably a good first approach in otherwise good-risk patients with no signs of portal hypertension or complication. There is a role for surgery as an initial attempt to control obstruction or jaundice in the patients.

The incidence of bile duct cancer in these patients, as I alluded to in the talk, was 11%. In the majority of patients this was not recognized before death, although in retrospect rapid progression in an otherwise stable patient should have suggested the diagnosis.

In our investigations we routinely do cholangiograms, endoscopic studies, and cytology. Surveillance of these patients is very important; especially in patients who are undergoing endoscopic procedures, a brush biopsy should be done.

In the Pittsburgh series about 10% of the 55 patients that they reported a couple of years ago were transplanted and found to have cancers. Because we have updated that series in the last few months, we have seen about a 10% incidence still.

The recurrence of disease in the transplant population has not been noted very frequently. We found it in one patient and as a transplant surgeon, I can assure you that it is very difficult sometimes to distinguish ischemic problems with liver transplantation from recurrent sclerosing cholangitis.

There is a role for early surgery in some of these patients, but I do think that regardless of what we do, these patients will develop a progressive problem and it will demand an ultimate treatment, and in this day and age I think that liver transplantation is the ultimate treatment.

There is a percentage of patients who will develop bile duct cancers, and these are often not recognized. Finally I think the role of nonoperative dilatation should be looked at more carefully in this population of patients.

From Monitoring to Predicting Outcome

It is the desire of all who take care of surgical patients to do it better. Certainly this is true for the modern surgeon and anesthesiologist who, working together in the operative period, have access to a great amount of physiologic data *via* current monitoring modalities. It is now routine to measure the patient's blood pressure, heart rate, cardiac rhythm, arterial hemoglobin saturation, expired CO_2, and temperature. In high-risk patients more data are usually available, such as pulmonary artery pressure, cardiac output, pulmonary artery mixed venous saturation, ST segment analysis, and transesophageal echocardiographic visualization of the heart. Finally computers are available to help in the recording, organization, analysis, and reporting of this wealth of physiologic information.

Because so much data now is available in a potentially useful way, it is important to identify those variables most important in predicting an adverse outcome. In this issue Charlson and coworkers report the patterns of intraoperative mean arterial pressure (MAP) that predict postoperative complications. They find that sustained (more than 60 minutes) decreases in MAP of ≥20 mmHg are associated with cardiac and renal complications in hypertensive and diabetic noncardiac surgical patients.

The authors are to be commended for their search for meaningful predictors of bad outcome, and the report has several significant strengths and limitations that should be discussed. First the patient population is a group of patients prone to postoperative complications. Hypertensive and diabetic patients have coronary and renal disease and are, therefore, a subgroup of the general surgical population in whom it would be useful to know predictors of morbidity and mortality. Hypertensive patients[1] and diabetics[2] have abnormal cerebral blood flow autoregulation. If this is true for the heart and kidney, then sustained hypotension could lead to hypoperfusion and possible ischemic damage. Diabetic and hypertensive patients, however, do not represent the majority of general surgical patients and generalization of the results of the Charlson study to that larger group of patients is problematic.

Second the authors have examined a single physiologic variable, MAP. Unfortunately blood pressure was obtained in a nonstandardized manner (three different methods used) and only at 5-minute intervals, thus possibly missing potentially important increases and decreases. Probably it is a valid observation that there is no difference in predictive value between the use of a 20-mmHg decrease and a 20% decrease from baseline because normal MAP for the patients under study ranges from about 70 to 110 and a 20% change would range from 14 to 22 mmHg—close to 20 mmHg. Also certainly it is not surprising that overall mean blood pressure is not a predictor of outcome because during most cases the blood pressure is kept as close to normal as possible by the anesthesiologist.

One perplexing finding regarding blood pressure is that although time at ≥20 mmHg mean arterial decrease is predictive of adverse outcome, greater decreases (*e.g.*, ≥40 mmHg) are not predictive. It is troubling that there seems to be no 'dose-effect' relationship of blood pressure to outcome, *i.e.*, the greater the decrease the worse the outcome. This suggests that MAP is not the only, or even the major, contributor to cardiac and renal morbidity in these patients. This conclusion is almost predictable because MAP is the product of systemic vascular resistance and cardiac output. A low MAP could reflect low resistance and/or low cardiac output. Low cardiac output is a product of reduced heart rate and/or reduced stroke volume. Stroke volume is influenced by preload and contractile function of the heart. Thus there are many possibilities for a reduced MAP, some of which are easily altered (or caused) by the anesthesiologist (*e.g.*, systemic vascular resistance and loading condition) and others might not be. The fact that so many variables affect this one measurement suggest that a simple cause-and-effect relationship between blood pressure and adverse outcome (20% reduced blood pressure causes bad outcome) may not hold in many settings.

A third consideration is use of observational analysis and logistic regression to predict outcome. The advantages and disadvantages of this form of analysis for predicting adverse postoperative outcome recently have been critiqued.[3] The investigators explored various patterns of MAP response, correctly using a logistic regression model. It is not clear if their model contained only the MAP pattern or the MAP pattern plus other significant covariates, such as diabetes, cardiac disease, and saline infusion. Appropriate use of logistic regression should provide information on the relative contribution of the multiple covariates. There are many other covariates available to the investigators that may predispose patients to adverse outcomes, but in logistic regression there is a limit to the number of variables that can be analyzed reliably. Harrell and colleagues[4] have suggested that no more than one covariate can be adequately analyzed for every 10 patients with the least frequent category of adverse outcome variable. Charlson and colleagues had 54 patients (21% of the study population) with an adverse outcome and 200 patients with no adverse outcome. Applying Harrell's 10-to-1 ratio would indicate that, at most, five covariates were analyzed reliably by Charlson and coworkers with their sample size of 200 patients. In an observational study, in which there are many pertinent uncontrolled factors, the number of covariates (age, blood pressure abnormality, HR changes, sex, surgery type, length of surgery, pre-existing comorbid conditions, and so on) to be analyzed may be large indeed and thus require a very large number of patients for the study to identify the important predictors of outcome. In short the sample size used by Charlson et al. is inadequate to accurately assess the relative importance of the several potentially important covariates.

Examples of two potentially important covariates are the length of surgery and heart rate changes. The length of surgery may be important not only because of its effect on outcome but also because it may impart a bias to the data. A patient with a short length of surgery is less likely to have a 60-minute episode of hypotension observed than a person with a long surgery simply because the short surgery might terminate before observing the full 60-minute episode. With regard to heart rate, it has been proved in patients with coronary artery disease, for example, that tachycardia is associated with ST evidence of ischemia.[5,6] In fact, in patients undergoing coronary artery bypass surgery, increase in heart rate is associated more with cardiac morbidity than with changes in blood pressure. Presumably this is so because tachycardia reduces oxygen supply not only by reducing the diastolic interval of cardiac perfusion but also by increasing myocardial oxygen demand at the same time.

Charlson and colleagues have implicitly recognized these problems when they state that the study should be done at multiple institutions. We would like to reinforce that sentiment with some added caveats. First the study should be done in a single-surgery type, or in multiple institutions across several specified surgery types with standardized surgery and anesthesia techniques. Second if MAP is a variable of interest, its measurement should be measured in a standardized way in all patients with sufficient time resolution to accurately measure the time course of events. Third the numbers of patients should be sufficiently large both to develop and test the logistic model. Fourth the analysis must extend beyond the few hours in the operating room to that greater amount of time after operation in recovery and/or intensive care. It is unlikely that hemodynamic events in the operating room are any more important than those during the entire perioperative period.

With the wealth of physiologic data and the electronic and computing capacity to meaningfully capture these data, it is important to use the appropriate statistical methods now available to us to predict deviations from acceptable values that lead to adverse outcome. With this knowledge surgery should be safer for our patients. Factors found during and after operation that affect outcome must be identified and thoroughly tested so the increasingly elderly and medically complicated patients we now care for can benefit from the type of important clinical research attempted by Charlson and coworkers. Monitoring in the perioperative period then will be more important in assuring optimal patient outcome.

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WHAT'S NEW IN GENERAL SURGERY

The Acutely Affected Abdomen in Paraplegic Spinal Cord Injury Patients

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The records of 145 paraplegic or quadriplegic patients were reviewed to identify those factors useful in the correct diagnosis of the acute abdomen in this population. Twenty-one patients had 22 episodes of acute or subacute abdominal problems. Presenting complaints, physical findings, and laboratory results were useful in various ways. However appropriate radiographic studies led to the correct diagnosis in 77% of patients. Although paraplegic and quadriplegic patients are predisposed to a distinct constellation of medical problems, including urinary tract infection and calculi, they also may present with other abdominal conditions that cause significant morbidity and mortality if not promptly recognized.

DURING THE LAST several decades, expertise in the management of spinal cord injuries has advanced considerably. As a result many more patients now survive the acute episode of spinal cord trauma, only to be left chronically para- or quadriplegic. In the United States, following the Vietnam War, there was a considerable increase in the number of paraplegics both in the Veterans Administration medical system and in the civilian population. The improved survival of soldiers suffering spinal cord injuries in this conflict was, in part, the result of rapid evacuation of the wounded to definitive care. Similarly, with the development of urban trauma centers during the last 20 years, we are witnessing improved survival rates of civilian patients with spinal cord injuries. This too has contributed to the increase in the number of paraplegic patients. Finally improved medical care of this patient population in general also has improved its longevity.

Each year approximately 10,000 new spinal cord injury patients are added to the estimated 200,000 paraplegics living in the United States, compared to only 100,000 in 1953.[1] Therefore we must be cognizant of the particular problems of diagnosis and treatment of surgical diseases in this group of patients.

Paraplegics are predisposed to a distinct constellation of medical problems, including urinary tract infections, renal calculi, and decubitus ulcers. Consequently what is often one of the more difficult problems in general surgery—the evaluation of the patient with an acute abdomen—becomes even more trying in paraplegic patients. The difficulty is further compounded by alterations in somatic sensation below the level of the patient's spinal cord lesion. The physician may be inclined to believe that it is impossible to correctly diagnose acute abdominal conditions in such patients but, in fact, it is usually possible to make such diagnoses rapidly and accurately.

The published literature provides little information regarding the reliability of various signs, symptoms, and laboratory tests in this population of patients. Therefore we reviewed our experience with paraplegic patients at the University of Arizona hospitals to identify those factors useful in the correct diagnosis of acute abdominal conditions.

Clinical Material

The charts of all paraplegic and quadriplegic patients admitted to the University of Arizona hospitals (University Medical Center and the Tucson Veterans Administration Medical Center) between 1978 and 1987 were reviewed. There were 145 such patients; of these, 21 had 22 acute or subacute abdominal problems (one patient had two distinct episodes). In this report frequencies of diagnosis and so on are expressed with a denominator of 22 episodes, unless otherwise indicated.

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TABLE 1. *Final Diagnoses*

Final Diagnosis	Number of Episodes
Cholecytitis or cholelithiasis	8
Perforated peptic ulcer	3
Renal disease	2
Other diagnoses	9
Appendicitis	1
Cecal volvulus	1
Small bowel obstruction	1
Carcinoid	1
Pancreatic cancer	1
Impaction	1
Discogenic disease	1
Upper GI hemorrhage	1
Unknown	1

GI, gastrointestinal

There were 1 female and 20 male patients; the mean age at time of spinal cord injury was 28 years (median age, 23 years). In 15 patients the cause of injury was recorded. These included seven motor vehicle accidents, and one each of trauma from a fall, diving accident, shrapnel injury, herniated intervertebral disc, gun shot wound, metastatic lung cancer, spina bifida, and poliomyelitis. Fourteen of the patients had a high cord lesion (T_7 or above), while seven had low cord injuries. This distinction is defined by the level of the splachnic outflow tract (T_8). All patients had past histories of urinary tract infections and four had previous episodes of urosepsis. Two patients had nephrolithiasis. Eight patients also had decubiti at the time of admission for their abdominal complaints.

The interval between the original spinal cord injury and hospitalization for the acute abdominal complaint ranged from 1 month to 36 years (mean interval, 15 years), with the mean age at presentation 43 years.

The most common surgical disease among our patients was acute cholecystitis, usually associated with cholelithiasis, diagnosed in 8 of 22 episodes (36%) (Table 1). The admitting diagnosis of one other patient was acute cholecystitis, but with further evaluation he was found to have pancreatic carcinoma with hepatic metastases. Three patients had perforated ulcers. Two patients had genitourinary disease requiring operation: a ruptured bladder in one and a renal abscess in the other. There were single cases of perforated appendicitis, cecal volvulus, small bowel obstruction, gastrointestinal carcinoid, impaction, gastrointestinal bleeding, and discogenic disease. The patient listed as 'unknown' had right lower quadrant pain that abated during a course of antibiotic therapy prescribed for lower extremity cellulitis. The patient with two abdominal episodes had a renal abscess and, later, cholecystitis.

Seven patients, one third of the group, had delays in diagnosis ranging from 1 day to 1 month (Table 2). One patient had cholecystitis diagnosed 1 month after presentation, following an extensive evaluation for genitourinary disease. In one patient, the diagnosis of perforated appendicitis was made at autopsy; he was being treated for presumed urosepsis when he died.

In 14 instances (64%), patients presented with complaints of abdominal or flank pain. This presentation was more common in patients with low cord lesions (6 of 7 patients [86%]), than in those with high cord lesions (8 of 14 patients [57%]). This pain was variously described as sharp and stabbing to dull and aching. Five patients (36%) with high lesions and two patients (28%) with low lesions experienced abdominal distention or tightness. Seven patients complained of shoulder pain (6 of 14 episodes [43%] in patients with high lesions, and 1 of 7 episodes [14%] in patients with low lesions). Five of the patients with shoulder pain had diagnoses other than cholecystitis. Autonomic dysreflexia (defined as hypertension; headaches; sweating of the forehead, face, and arms; and tachycardia or bradycardia) was described in only three patients (with diagnoses of perforated duodenal ulcer, cecal volvulus, and cholecystitis). Seven of our patients were febrile, with temperatures on admission ranging from 98.3 to 103.1 F.

Physical examination often was not helpful. In eleven instances, patients were tender to palpation of the abdomen. Seven of these patients had high cord lesions and four had low cord lesions. Six patients were noted to be distended, all with high cord lesions. Only four patients were recorded as having decreased or absent bowel sounds.

TABLE 2. *Delay in Diagnosis*

Presumptive Diagnosis	Final Diagnosis	Delay	Comment
Urosepsis or nephrolithiasis	Ruptured bladder	5 days	Developed dysreflexia
	Cholecystitis	1 month	Diagnosed by OCG
	Perforated appendicitis	6 days	Diagnosed at autopsy
Colonic neoplasm	Carcinoid	4 days	Diagnosed by CT scan, confirmed by biopsy
Hepatitis	Cholecystitis	1 week	Diagnosed by OCG
Sepsis	Perforated ulcer	1 to 2 days	Free air on CXR
No abdominal problem	SBO with infarction	2 days	Feculent vomiting prompted evaluation

SBO, small bowel obstruction; OCG, oral cholecystogram; CT, computed tomogram; CXR, chest x-ray.

Increased rigidity or spasm was noted in three patients, all with high cord lesions. Four patients (three with high and one with low cord lesions) were neither tender nor distended. Rectal examination proved helpful only in the patient with GI hemorrhage.

Leukocytosis was documented in 12 patients, with a left shift present in eight patients. Mild to moderate elevations in liver function tests were found in three of the eight patients with cholecystitis. All of our patients had white cells (from 6 to more than 100 per high-power field) in their urine.

Radiographic studies, including chest films, abdominal series, oral cholecystograms (OCG), CT scans, sonograms, and barium studies, led to the correct diagnosis in 17 episodes (77%) (Table 3). One patient, who had the final diagnosis of chronic constipation, had a normal abdominal series, barium enema, and OCG. The patient with gastrointestinal hemorrhage and the one with right lower quadrant pain of unknown etiology had no radiographic studies. All patients with cholecystitis and cholelithiasis had either nonvisualization by OCG or gallstones visualized by ultrasound. The three patients with perforated ulcers had free air on chest or abdominal radiographs. A ruptured bladder was diagnosed by retrograde cystography. The patients with pancreatic cancer and carcinoid syndrome had masses discovered by computed tomographic scan. The cecal volvulus was diagnosed by plain abdominal films and confirmed with a barium enema. The patient with intestinal obstruction had dilated loops of small bowel with air–fluid levels on plain abdominal films.

Of the 22 episodes of abdominal pain, 17 came to operation. The eight patients with cholecystitis or cholelithiasis underwent cholecystectomy; two required common bile duct exploration for filling defects detected by intraoperative cholangiography. Two of the three patients with perforated ulcers had an omental patch or oversewing of the ulcer. The third patient, who had diffusely metastatic lung cancer, was not explored. At autopsy a gastric ulcer was found. Other operations, along with the definitive diagnostic test, are listed in Table 3. Three patients did not require operative intervention; their final diagnoses were upper gastrointestinal hemorrhage, discogenic disease, and right lower quadrant pain of undetermined etiology.

Two patients died without operative intervention. One patient died of perforated appendicitis, and one patient with terminal lung cancer was not explored, yielding an overall mortality rate of 10%. There were no operative deaths. Of the patients undergoing operation, eight patients (38%) experienced morbidity. Two patients had more than one complication. Three patients had postoperative temperatures to 102 F attributed to atelectasis. Two patients had postoperative urinary tract infections (one Pseudomonas, and one candida) and one had postoperative urinary retention when his suprapubic catheter became occluded. Other complications included a wound infection and a prolonged ileus lasting approximately 1 week after operation. One patient who had a normal intraoperative cholangiogram had elevated liver enzymes after cholecystectomy. These resolved spontaneously. One patient presented 1 year after cholecystectomy with a partial small bowel obstruction; this resolved with nonoperative treatment.

The time from operation to tolerating a normal diet was accurately recorded in 15 of our patients and ranged

TABLE 3. *Radiologic Evaluations and Operative Procedures (Number of Patients)*

Final Diagnosis	Definitive Test	Operation
Cholecystitis or cholelithiasis (8)	U/S (4), OCG (5) (one pt had both)	Cholecystectomy (8) with CBDE (2)
Perforated peptic ulcer (3)	CXR (2) KUB (1)	Patch (2) No operation (1)
Genitourinary disease (2)		
Ruptured bladder	Cystogram	Repair
Renal abscess	IVP	Drainage
Cecal volvulus	Barium enema	Right hemicolectomy
Small bowel obstruction	Plain abdominal films	Enterolysis
Carcinoid	CT scan	Laparotomy and biopsy
Pancreatic Carcinomia	U/S, CT scan	Laparotomy and bypass
Perforated appendicitis	Autopsy	None
Impaction	Plain abdominal films, Barium enema	None
Discogenic disease	OCG, U/S (normal)	None
GI hemorrhage	Rectal exam	None
Unknown	None	None

U/S, ultrasongram; OCG, oral cholescystogram; CXR, chest x-ray; IVP, intravenous pyelogram; CT, computed tomogram; CBDE, common bile duct exploration; GI, gastrointestinal.

from 3 to 10 days (mean 5 days). It was difficult to assess hospital stay in our patients because several of them were hospitalized for extended periods.

Discussion

Our purpose in this study was to identify those signs, symptoms, and laboratory studies that proved useful in making the rapid and accurate diagnosis of acute abdominal conditions in paraplegic patients.

At the turn of the century, the mortality rate from abdominal conditions in patients with spinal cord injuries ranged from 50% to 86% in a series reported by Burrell from Boston City Hospital. By the end of World War I, however, the mortality rate had dropped to 27%. In the 1950s, several series reported mortality rates of 10%.[2] This has declined little to the present time, with most centers reporting mortality rates of 5% to 8% and morbidity rates of 30% to 50%.[3] These rates are thought to be higher than those of the general population because of delays in diagnosis. Too often the tendency is to attribute nonspecific abdominal pain, nausea, vomiting, and fever in paraplegics to complications of the genitourinary system, particularly pyelonephritis and renal calculi. While both are common in such patients, it is important to rule out other potentially serious illnesses.

In paraplegic patients, somatic sensation is severely disrupted due to interruption of pain transmission along the spinal cord at the site of injury. However often it is not completely absent. Chronic paraplegics may have some sensation over their anterior abdominal wall. One reason for this is that the spinal injury is often the result of blunt trauma in which the cord is damaged not by transsection of fibers but by contusion, compression, edema, and thrombosis of spinal arteries and veins, resulting in dysfunction of most, but not necessarily all, fibers. Some isolated pathways often remain.

While somatic sensation is severely altered in paraplegia, visceral sensation is often well preserved. Several explanations have been suggested.[4–7] Visceral sensory fibers ascend several levels along the autonomic ganglia before entering the cord and thus may simply bypass the spinal cord lesion.[4] Alternatively visceral sensory fibers may travel with the vagus nerve, likewise bypassing the cord lesion. Finally some visceral pathways may course intact through the level of injury. The precise mechanism actually may represent an amalgamation of these theories.

Physical examination of the abdomen is unreliable in the paraplegic patient because of the law of the spinal cord:"If one sustains a lesion to the spinal cord, at the level of injury there will never be a return of reflex activity, but when spinal shock disappears, there will be a return of reflex activity in every segment below the level of injury."[8]

Thus, as long as the reflex arc is intact, an upper motor neuron lesion results in spastic paralysis of the striated muscles of the abdominal wall, causing chronic contraction and spasm of the abdominal wall musculature. The clues to the presence of parietal peritoneal inflammation on which surgeons rely, such as guarding and muscular rigidity, are obviously not valid parameters in such patients.

How then does one evaluate the acute abdomen in paraplegic patients? Among the signs and symptoms that have been cited as useful are abdominal pain, tenderness or distention, changes in spasticity of abdominal or lower extremity musculature, and autonomic dysreflexia.[3–5,8–16] The last is characterized by hypertension; headaches; sweating of the forehead, face, and arms; tachycardia (in patients with cervical lesions), or bradycardia (in patients with high thoracic lesions). Other complaints and findings cited as useful include fever, anorexia, nausea, vomiting, or diarrhea, the 'feeling that something is wrong,' bladder spasms, tachycardia, and referred pain, especially shoulder pain.[3,8,17,18] Laboratory findings cited as diagnostically helpful are leukocytosis, especially when accompanied by immature forms; abnormalities of the urinalysis; abdominal films showing pneumoperitoneum, volvulus, or obstruction; and abnormal findings on IVP. Unfortunately many of these findings, including autonomic dysreflexia, are not infrequently seen in the 'healthy' paraplegic patient.

Most similar series reported in the literature are limited to two to seven patients.[4,5,9–16,18] Only two series with more than 10 cases have been reported; both of these are from the Long Beach Spinal Cord Center.[3,8] Excluding the two Long Beach series, 50 cases with the following pathologic diagnoses have been reported: perforated peptic ulcer (n= 14), appendicitis (n = 10), small or large bowel obstruction and/or volvulus (n = 7), perforated colon or rectum (n = 6), constipation or impaction (n = 3), renal stones (n = 3), cholecystitis (n = 2), ruptured bladder (n = 1), renal abscess (n = 2), and other causes (n = 2). In the more recent report from Long Beach,[3] there were 10 cases of appendicitis, 16 of intestinal obstruction, 3 of bladder perforations, 1 of ruptured spleen, and 1 case of cholecystitis.

In the Long Beach series, the presence of autonomic dysreflexia correlated well with the diagnosis of abdominal catastrophe in patients with high lesions; 92% of such patients with significant intra-abdominal disease had autonomic dysreflexia.[3] Patients with low lesions typically (92%) had many of the signs and symptoms of an acutely affected abdomen and could localize their pain to a specific quadrant. Anorexia was one of the earliest symptoms associated with visceral pain (in 84% of patients). The authors note that even patients with high lesions often can localize pain, presumably through referred pain mechanisms.

While the presence of autonomic dysreflexia was a prominent finding in the Long Beach series, it has not been mentioned in other reports, except as a change in abdominal wall spasticity or reflexes. This may, however, simply reflect less awareness of this entity in general hospitals. Shoulder pain was, however, mentioned in several reports as an important indicator of abdominal disease.[3,8,17,18] Other diagnostic evidence often was only helpful when the patient's 'normal' state was known. Quite often the patient would report that 'something was wrong' but could not further localize the pain or discomfort.

The only change in vital signs consistently of value in other series was a temperature of more than 103 degrees F, which correlated well with the presence of renal disease. Radiographic studies were mentioned in a few series; however none suggested that they would prove to be as helpful as they were in our series.

In our patients the presenting complaints, physical examination, and laboratory results were useful in various ways (Table 4). In patients with high lesions, abdominal pain, shoulder pain, and bloating were common complaints. Abdominal tenderness and distension on physical examination, if present, were helpful findings in these patients. In contrast to the Long Beach review, autonomic dysreflexia was present in only three of our patients (21%), all with high lesions. In patients with low cord lesions, complaints of abdominal pain were frequent, while complaints of shoulder pain and bloating were uncommon. Abdominal tenderness was again helpful, if present. Of note the abdomens of four patients were not tender to palpation, despite complaints of abdominal pain; three had high lesions and one had a low lesion.

TABLE 4. *Symptoms and Signs in Spinal Cord Injury Patients*

	Incidence	
Symptom or Sign	High Lesion (%)	Low Lesion (%)
Abdominal pain	57	86
Bloating	36	28
Shoulder pain	43	14
Autonomic dysreflexia	21	0
Abdominal tenderness	50	57
Abdominal distension	43	0
Rigidity/spasticity	21	0
No tenderness	21	14

Leukocytosis was documented in only 55% of episodes; in 36% of the cases a leftward shift was present, a surprising finding given the severity of the intra-abdominal disease. Clearly significant intra-abdominal disease can be present in these patients without an increase in or leftward shift of the white blood cell count. Often the urinalysis also was misleading. Pyuria was present in all our patients but in only two patients did urinary tract disease prove to be diagnostically important. Two other patients had postoperative urinary tract infections; their preoperative pyuria may have suggested an active infection. Nevertheless the finding of pyuria often mistakenly diverted attention to the patient's genitourinary system, resulting in unnecessary delays in the diagnosis of intra-abdominal disease.

In our experience radiographic studies proved the most useful (Table 3). All patients with cholecystitis had positive findings by OCG or ultrasound. Every patient with a perforated ulcer had free air within the peritoneal cavity by plane films of the abdomen or upright chest films. In the other patients, radiographic studies, including CT scans, barium studies, and intravenous pyelograms (IVP), often led to the correct preoperative diagnosis of intra-abdominal disease. Overall 77% of the patients were correctly diagnosed radiographically.

Based on this experience, we recommend that in paraplegic patients with complaints of abdominal or shoulder pain, gastrointestinal symptoms, or abdominal tenderness, an aggressive search be made for the underlying etiology. At the time of admission, plane films of the abdomen should be obtained. If these are nondiagnostic, abdominal ultrasonography to detect cholelithiasis or intra-abdominal abscess is recommended. Barium enema, IVP, and CT scans of the abdomen often are helpful and should be pursued as needed.

The paraplegic patient with abdominal complaints presents a diagnostic dilemma. Altered perception of pain and underlying chronic disease, such as urinary tract infection and calculi, often make diagnosis difficult. Based on our experience and a review of the literature, we suggest that the following are most helpful in diagnosing abdominal pathology: shoulder pain, the patient's 'feeling that something is wrong,' change in spasticity or autonomic dysreflexia, and most importantly, appropriate radiographic studies. The physician should be wary of initially ascribing these findings to genitourinary tract disease; other abdominal conditions can cause significant morbidity and death if they are not promptly recognized.

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Laparoscopic Cholecystectomy

When stones are identified in the cystic and common ducts during laparoscopic cholecystectomy, they can be successfully fragmented at the time of surgery, eliminating need for a second postoperative procedure. A small, flexible endoscope can be passed into the cystic and common ducts. The laser fiber is advanced through the scope until it contacts the stone and the laser is activated. Stone fragments are pushed through the sphincter into the duodenum and, when necessary, removed with small baskets or grasping instruments.

Endoscopic Retrograde Cholangiopancreatography

Stone fragmentation via ERCP can be done under direct or fluoroscopic vision. A laser fiber can be advanced into the common duct using either small endoscopes or radiopaque laser fiber catheters. The laser fiber tip is advanced beyond the end of the delivery device until it is in contact with the stone. After position is verified either fluoroscopically or by direct vision, the laser is activated. The procedure continues until fragments are small enough to pass through the sphincter. Frequent irrigation of the bile duct is performed to wash away debris into the duodenum. Larger fragments can be retrieved by standard baskets or occlusive balloons.

Percutaneous Choledocholithotomy

Duct calculi are accessed through a T-tube, using a flexible endoscope. After visualization, the laser fiber is advanced through the working channel of the endoscope until it is in contact with the stone. After position verification, the laser is activated and stone fragmentation occurs under direct vision.

This procedure can also be performed under fluoroscopy using radiopaque laser fiber catheters or baskets designed with a central channel to accommodate the laser fiber.

Open Cholecystectomy

During open gallbladder removal, stones are frequently identified in the common, cystic or hepatic duct. Using a choledochoscope under direct vision, the laser fiber is placed against the stone and the laser is activated. Fragments can be removed in a retrograde fashion or pushed through the sphincter into the duodenum.

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Lasertripsy has proven effective in treating stones in the gallbladder. Currently, there are two approaches. Percutaneous cholecystolithotomy provides a direct, frontal approach into the gallbladder. As an alternative, a percutaneous transhepatic approach can be implemented using a small caliber flexible endoscope.

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- Laparoscopic Cholecystectomy
- Endoscopic Retrograde Cholangiopancreatography (ERCP)
- Percutaneous Choledocholithotomy
- Open Cholecystectomy

GALLSTONES
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Summary

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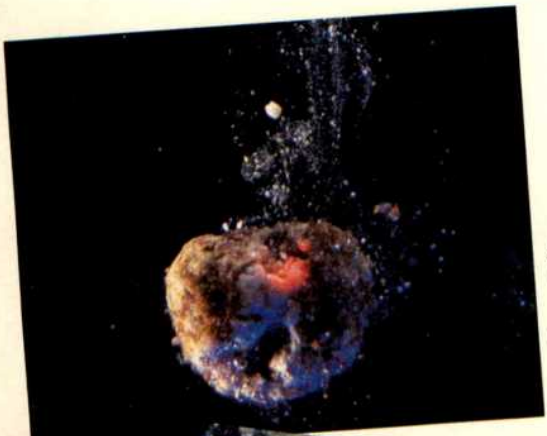

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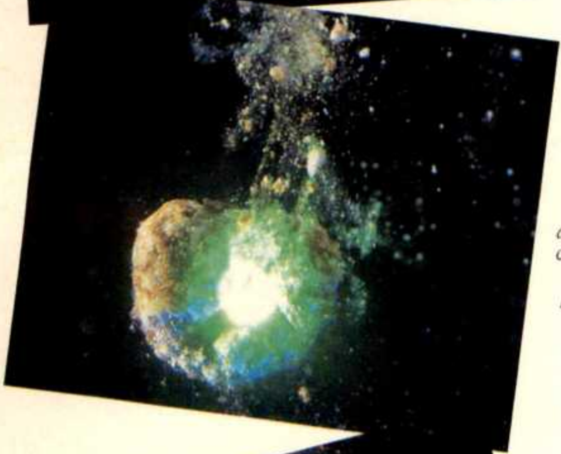

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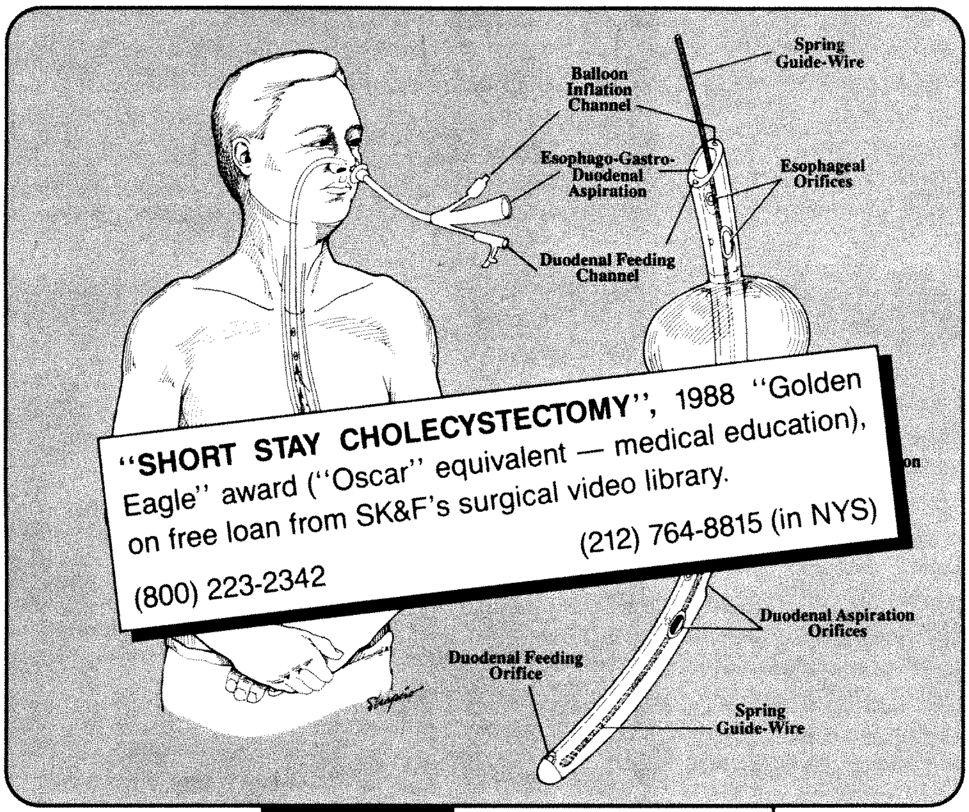

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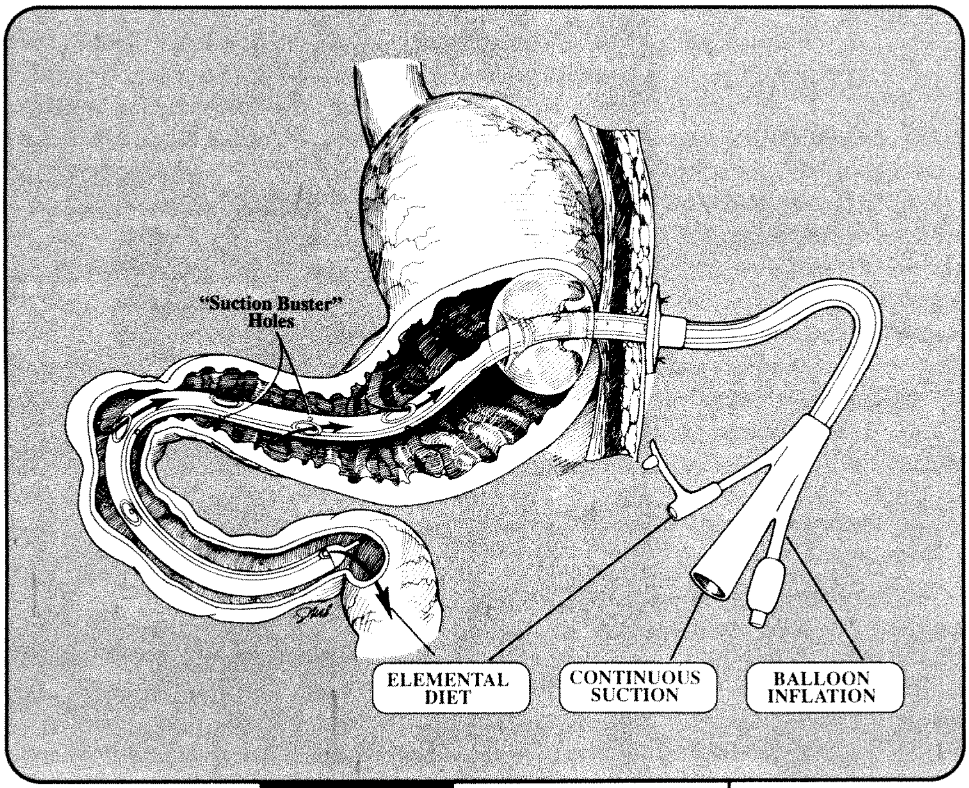

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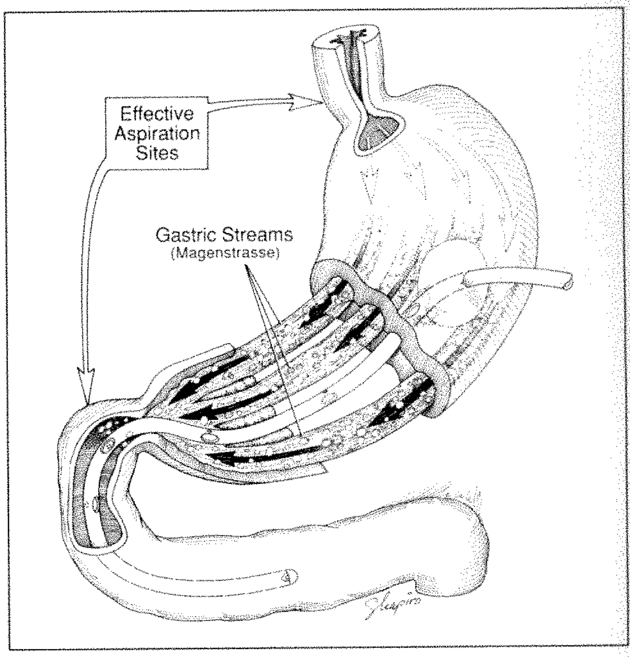

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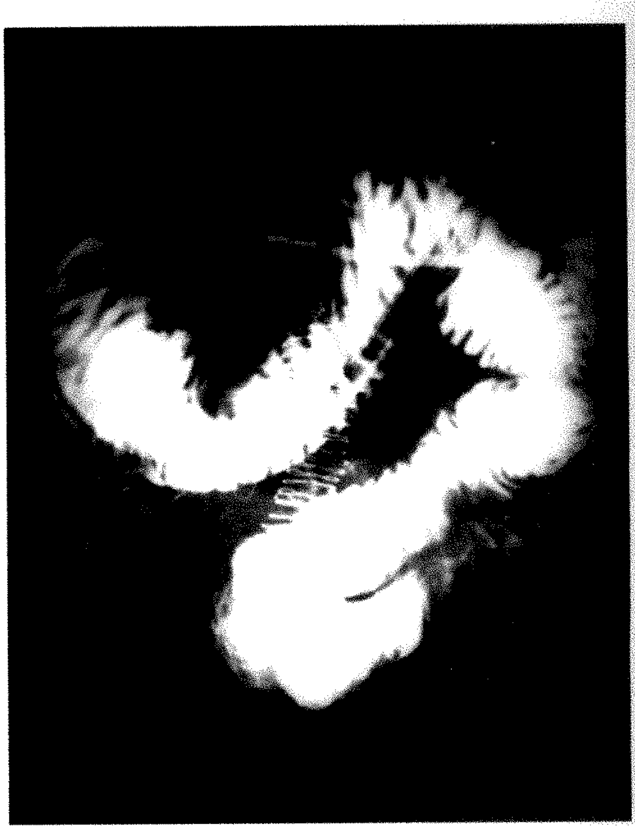

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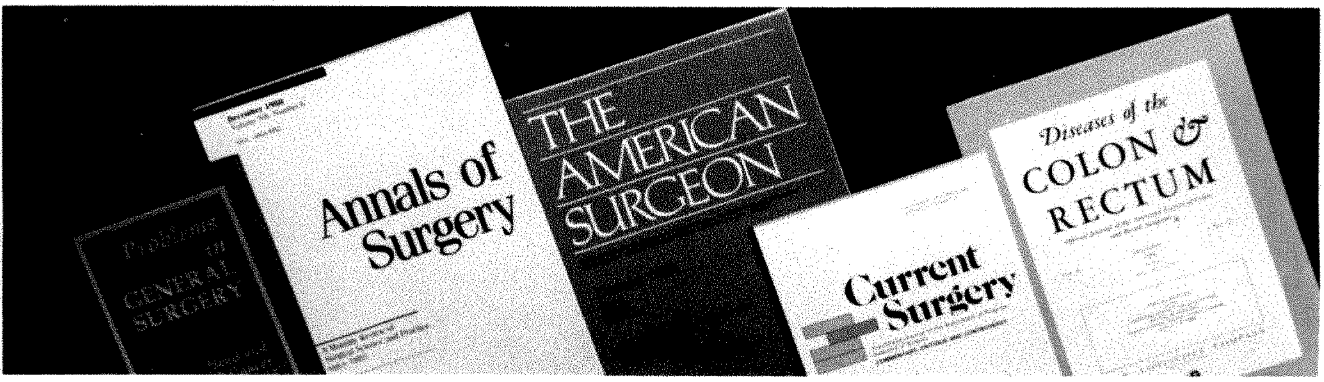

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While monitoring blood pressure is a routine part of intraoperative management, several methods have been proposed to characterize intraoperative hemodynamic patterns as predictors of postoperative complications. In this prospective study of a high-risk population of hypertensive and diabetic patients undergoing elective noncardiac surgery, one objective was to compare different approaches to the assessment of intraoperative hemodynamic patterns to identify those patterns most likely to be associated with postoperative complications. Twenty-one per cent of the 254 patients sustained cardiac or renal complications after operation. Patients with more than 1 hour of ≥20-mmHg decreases in mean arterial pressure (MAP) or patients with less than 1 hour of ≥20-mmHg decreases and more than 15 minutes of ≥20-mmHg increases were at highest risk for postoperative complications. Together these two patterns had a 46% sensitivity rate and a 70% specificity rate in predicting postoperative complications. Using 20% change in intraoperative MAP produced results nearly identical to 20-mmHg changes. When the duration of 20-mmHg changes was accounted for, changes of a greater magnitude (*e.g.*, 40 mmHg) were not significant independent predictors of complications. The use of the mean difference from preoperative MAP was misleading because patients who experienced both high and low MAPs tended to have nearly normal mean MAPs, but high complication rates. The absolute magnitude of intraoperative MAPs, regardless of the preoperative levels, also was evaluated. The overall mean intraoperative MAP was not a significant predictor of complications. Specific intraoperative MAPs (*e.g.*, less than 70 mmHg and more than 120 mmHg) also were evaluated. While neither was a significant predictor, there was a trend for increased complications among patients whose MAPs decreased to less than 70 mmHg. Intraoperative blood pressure should be analyzed in relation to the patient's preoperative blood pressure. Prolonged changes of more than 20 mmHg or 20% in relation to preoperative levels were significantly related to complications.

For many years, anesthesiologists have recorded blood pressure and pulse every 5 minutes during operations. While these recordings are reviewed routinely by internists and surgeons to determine if their patients experienced clinically important intraoperative changes in blood pressure, the criteria for assessing intraoperative blood pressure vary widely in clinical practice and research.

In previous studies we found that the duration of changes of ≥20 mmHg in intraoperative mean arterial pressure (MAP), as well as preoperative characteristics and other intraoperative events, were significant predictors of postoperative congestive heart failure (CHF), myocardial infarction and ischemia, and renal dysfunction.[1-3] In other studies, investigators have defined change as a 20% to 30% decrease or increase in systolic pressure for more than 10 minutes,[4-9] as a 20% increase or decrease in MAP,[10] or as a 20- to 50-mmHg decrease in blood pressure.[11-13] Others have evaluated the actual MAP[14] or determined whether the systolic pressure was greater than 180 to 200 mmHg or less than 80 to 90 mmHg, or the diastolic pressure was more than 110 mmHg.[4,7,15] Some have reported the rate–pressure product,[16,17] while others have argued that this product is misleading.[18,19]

From a practical perspective, the issue concerns the optimal method to assess intraoperative changes in MAP. Would it be preferable to examine the absolute, percentage, or mean change in MAP, the overall mean intraoperative pressure, or the absolute intraoperative pressures regardless of preoperative MAP? To address this question,

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the clinical significance of changes in intraoperative blood pressure and pulse must be judged by their sensitivity and specificity as predictors of postoperative complications. Therefore this paper considers all renal and cardiac complications as relevant outcome events. Different approaches to the assessment of changes in intraoperative blood pressure and pulse are compared to ≥20-mmHg differences in MAP and ≥20 beat-per-minute differences in pulse as predictors of postoperative cardiac and renal complications.

Methods

Assembly of Study Population

All patients who had essential hypertension (high blood pressure) or diabetes mellitus who were undergoing elective general surgery were eligible for enrollment. The criteria for hypertension were treatment with any medication explicitly used to reduce blood pressure, which included all patients aged less than 30 years (n = 171); or for patients aged 30 years or older, a systolic ≥160 mmHg or diastolic ≥95 mmHg (n = 30). None of the patients had mean preoperative diastolic pressures more than 110 mmHg. Patients with secondary hypertension (*i.e.*, adrenocortical, proved renovascular hypertension, and so on) were excluded. The criteria for diabetes were (1) treatment with insulin or oral hypoglycemic agents before admission (n = 92), including treatment started during preoperative evaluation; and (2) elevated fasting glucose levels (plasma ≥140 mg/dL; whole blood ≥120 mg/dL) on more than one occasion before operation (n = 16). Patients who developed hyperglycemia after operation without meeting either of these criteria were not classified as diabetic.

Between July 1982 and September 1985, 278 patients were enrolled. Patients undergoing any elective general surgery were eligible for enrollment, including intra-abdominal procedures, peripheral vascular or aneurysm surgery, or other operations such as amputation or hemorrhoidectomy. To record the number of patients who were eligible but not entered, the anesthesiologists prospectively documented which patients undergoing general surgery during the study interval had hypertension and diabetes; unfortunately these records were inadvertently destroyed. Therefore to estimate the proportion of eligible patients who were entered into the study, we selected two types of operation (vascular surgery and cholecystectomy); the charts of all 1398 patients undergoing these operations during the same secular interval were reviewed. These operations accounted for 40% of the surgery performed in the prospective study. Of the 1398 patients who had a cholecystectomy or vascular surgery, 26% of eligible hypertensives and 34% of eligible diabetics were entered into the prospective study.[18]

Preoperative Evaluation

The protocol was reviewed and approved by the Institutional Human Rights Committee. Informed consent was obtained from all patients. Before operation basic demographic and clinical data were recorded and a physical examination was performed in a standardized manner.[20] The patient's right and left arm sitting blood pressure and pulse, as well as the recumbent and standing pulse and blood pressure were obtained. Blood pressure was recorded using a standard mercury manometer; Korotkoff Phase V was recorded as the diastolic pressure. The cuff was placed so that the lower margin was 2 to 3 cm above the antecubital space, with the bladder over the medial surface of the arm.[21] Blood pressures were obtained every 4 hours before surgery by the nursing staff. These systolic and diastolic blood pressures were recorded to delineate the patient's usual preoperative MAP, the standard deviation, and the minimum and maximum values.

Intraoperative Monitoring

On the day of surgery, a research assistant, blinded to the hypotheses of the study, recorded pulse and blood pressure immediately before induction, immediately after the induction agents were given, and immediately after intubation (the actual interval between these events varied from patient to patient), and every 5 minutes thereafter. The method of intraoperative blood pressure measurement was ultimately the decision of the anesthesiologist. In 52 patients intra-arterial measurements were made using a 20-gauge teflon catheter in the radial artery and connected to a Marquette 7000 (Marquette Electronics, Milwaukee, WI) dual pressure monitor calibrated before each use (accuracy of ± 1 mmHg); 71% of the patients who had an intra-arterial catheter were undergoing vascular surgery. The use of an indirect automatic device, the Omega 1000 (Vivo Research Labs, Tulsa, OK) (an accuracy of ±2 mmHg), which has been shown to generate reproducible and valid measurements of blood pressure while used in the operating room,[22] was encouraged in the remaining patients. The anesthesiologist actually used the indirect recorder in 72 patients. In 130 patients the anesthesiologist decided to use a standard mercury manometer instead of the Omega 1000; in these cases the research assistant obtained and recorded the blood pressures according to the procedures described previously. The proportion of the patients who had indirect device *versus* a mercury manometer did not differ according to the age of the patient, cardiac disease, the severity of hypertension, or diabetes. The indirect device was used more commonly in patients whose surgery lasted more than 2 hours ($p < 0.05$).

Standard electrocardiogram monitoring was performed during all operations. The research assistant recorded all pharmacologic agents used during each 5-minute interval of the operation. The use of anesthetic agents and adjuvants was recorded. Major intraoperative events, such as skin incision, reversal of anesthesia, aortic cross-clamping, drainage of ascites, and changes in position also were recorded.

In 24 patients (8.6%), the research assistant was not present in the operating room to record events and blood pressures. Because the purpose of this analysis is to assess the intraoperative blood pressure and pulse in relation to cardiac and renal complications, we have omitted these 24 patients (seven of whom had complications) because the intraoperative data was not recorded by an independent observer. The remaining sections of this paper will concentrate on the 254 patients for whom intraoperative data were recorded by an independent observer.

Postoperative Follow-up

All patients were followed daily for 7 days after operation or until death, discharge, or reoperation, with clinical examinations, serum creatinine measurements, electrocardiograms, and creatine kinase isoenzyme measurements. All the events and evidence were prospectively documented by physicians and/or research assistants.

After discharge the evidence was reviewed for all patients who developed dyspnea, palpitations, chest pain, signs of CHF, electrocardiographic changes, elevated CK-MB levels, or increased serum creatinine levels (by 0.4 mg/dL) by two physicians who were blinded to the patient's preoperative status and intraoperative course. These physicians determined whether the patients who were suspected of having myocardial ischemia, blood pressure, or postoperative renal impairment met the diagnostic criteria.[23,24]

Definition of Outcomes

A cardiac death was a death in the setting of myocardial ischemia, infarction, ventricular tachycardia, or cardiogenic shock, with the clinical events leading to death compatible with a primary cardiac etiology.

Most of the cardiac deaths, arrests, or myocardial infarction or ischemia occurred within the first 3 days after surgery, with the risk declining sharply after the second postoperative day; events occurring after the sixth postoperative day were not counted as postoperative complications.

The diagnosis of postoperative pulmonary edema required a pulmonary capillary wedge pressure of more than 20 cm H_2O (pulmonary artery catheters were placed in all patient suspected of having pulmonary edema) and a typical roentgenologic image showing pulmonary edema. The diagnosis of postoperative congestive heart failure required at least two of the following: S_3 gallop, typical roentgenologic image, bibasilar rales involving more than one third of the lung fields, or an elevated central venous pressure (more than 18 cm H_2O). Congestive heart failure was considered a postoperative complication only if it began within the first 3 postoperative days. Heart failure began on the day of operation in 6 patients, on the first postoperative day in 1 patient, and on the second postoperative day in 6 patients.

Postoperative renal dysfunction was defined as an increase in the serum creatinine level of ≥20%, persisting for 48 hours or more, which began in the first 3 days after surgery. In identifying patients whose serum creatinine levels remained persistently elevated at discharge from the hospital, an increase in the serum creatinine of ≥20% persisting for more than 48 hours had a true-positive rate of 93% and a false-positive rate of 7%.[24] Increases of ≥20% in creatinine level that began on the fourth postoperative day or thereafter could not be attributed to intraoperative events and were not considered in this analysis.

Analysis

To standardize the definition of the MAPs with the different techniques, MAPs were calculated as the diastolic pressure plus one third (systolic–diastolic). The primary analysis of intraoperative blood pressure was based on the differences between intraoperative MAPs and preoperative MAPs. The preoperative pressures all were obtained by mercury manometer and the intraoperative pressures were obtained by mercury manometer, intra-arterial catheter, or indirect oscillometric device. Intraoperative pressures obtained by manometer therefore were not adjusted because they were obtained by the same method. The MAPs obtained by the Omega 1000 *versus* mercury manometer, after adjusting for differences between arms, were 0.4 mmHg lower than the mercury manometer pressure, so 0.4 mmHg was added to all pressures obtained using the Omega device (the 95% confidence interval was −0.6 to +1.3 mmHg).[21]

The difference between the intra-arterial direct MAPs and the mercury manometer pressures, as expected, were greater; the mean intra-arterial pressure was 3.4 mmHg lower than simultaneous assessments with a mercury manometer (95% confidence interval: −5.1 to −1.6 mmHg); thus, for the adjustment, 3.4 was added to all intraoperative pressures obtained by arterial catheter. The correlation between indirect measurements and intra-arterial measurements may differ substantially from patient to patient, although the differences do not increase with age.[25] It would have been preferable to adjust for the intrapatient differences. In 25 of the 51 patients with arterial catheters, detailed calibrational data were available for such intrapatient adjustments; in the others it was not available. For the patients in whom it was possible to make the intrapatient adjustments, the hemodynamic patterns were re-evaluated using the patient-specific adjustments. These adjustments did not significantly alter the classification of patients according to 20-mmHg changes or other classifications.

Logistic regression was performed using the CATMOD program that uses the maximum likelihood method in SAS.[26] The likelihood ratio compares the specified model with the unrestricted model and is a goodness-of-fit test and was used to compare the overall predictive ability of the different models.[26] The chi square test for each effect is a Wald test based on the information matrix from the likelihood calculations and is the basis for the reported levels of statistical significance.[27] Each potential cutoff point for alternate methods of characterizing the intraoperative hemodynamic course (*e.g.*, a decrease in MAP to less than 70 mmHg) was initially examined in a simple model to determine the optimal duration to use as a cutoff point for that variable considered alone. Once the optimal cutoff point was determined, multiple logistic regression was used to determine the contribution of that variable at its optimal cutoff *versus* the definitions of change in intraoperative MAP based on the 20-mmHg strata defined previously. To account for potential confounders, those covariates that were found previously to be significant predictors of cardiac and renal complications (preoperative cardiac disease, diabetes, and less than 300 cc per hour of intraoperatively administered saline-containing fluids) were entered into the models designed to test the contribution of different methods of characterizing the intraoperative hemodynamic pattern.

Results

Among the 254 patients, 4% (10) had life-threatening complications: 3 had cardiac death; 2 had pulmonary edema and cardiac arrest; 2 had myocardial infarction and cardiac arrest; and 3 had definite or probable myocardial infarction. In addition 4% (10) of patients had postoperative CHF. Seven per cent of patients had a possible myocardial infarction (2) or definite myocardial ischemia with electrocardiogram changes (18); 12 of these patients had elevated CK-MB levels, and the eight patients without ≥3% CK-MB levels had ST-T changes that persisted more than 48 hours. In addition one patient had unstable angina without electrocardiographic changes and two patients had definite angina by the Rose criteria. Six per cent (16) had postoperative renal dysfunction. In total 21% of patients (54 of 254) had at least one cardiac or renal complication.

We originally defined intraoperative hypotension or hypertension as operative increases or decreases of ≥20 mmHg in MAP from the patient's preoperative MAP. Intraoperative hypotension lasting 60 minutes or longer and intraoperative hypertension lasting 15 minutes or more in combination with hypotension lasting less than 60 minutes were significant predictors of ischemic cardiac and renal complications.[1–3] In addition postoperative myocardial infarction or ischemia occurred significantly more often among patients with a previous infarction or cardiomegaly on chest radiograph.[3] Postoperative renal dysfunction occurred significantly more often among patients with decompensated CHF and among those who received less than 300 cc/hour of saline-containing fluids during operation.[1] Postoperative CHF occurred significantly more often in patients with cardiac disease, especially diabetics, and more frequently in patients who had ≥20 mmHg, but especially ≥40-mmHg changes in intraoperative MAP.[2] Therefore, considering the preoperative status of the patients, changes in intraoperative MAP ≥20 mmHg have been shown to be a significant predictor of postoperative cardiac and renal complications.

Because this definition differs from those most often used in clinical practice and clinical research, the subsequent analysis is designed to compare the predictive ability of different strategies for characterizing intraoperative hemodynamic patterns to predict postoperative complications.

20-mmHg Changes in Intraoperative MAP

In total 62% of patients experienced at least 5 minutes of ≥20-mmHg intraoperative decrease in MAP below their preoperative MAP. The duration of the 20-mmHg decreases was important in predicting complications: 31% of patients with decreases lasting more than 1 hour had complications compared to 17% of those with decreases lasting less than 1 hour. In comparison 17% of patients without such decreases had complications. At any cutoff point less than 1 hour, patients with a longer duration of ≥20-mmHg decreases had higher complication rates than patients with those of shorter duration; however 1 hour was the optimal cutoff as judged by likelihood ratios. When other significant predictors of postoperative complications (*e.g.*, cardiac disease, diabetes, cardiomegaly, and intraoperative fluid management) were accounted for using logistic regression, more than 1 hour of MAP decreases of more than 20 mmHg was a significant predictor of postoperative complications ($p < 0.04$).

In addition 62% of patients experienced at least 5 minutes of ≥20-mmHg intraoperative increases in MAP above their preoperative MAP. The duration of 20-mmHg increases was important in predicting complications: 50% of patients who had ≥20-mmHg increases lasting 60 minutes or longer had complications compared to 19% for those with increases lasting less than 1 hour. In contrast 22% of patients who did not have 20-mmHg increases had complications. Logistic regression confirmed that 1 hour of ≥20-mmHg increases was a significant predictor

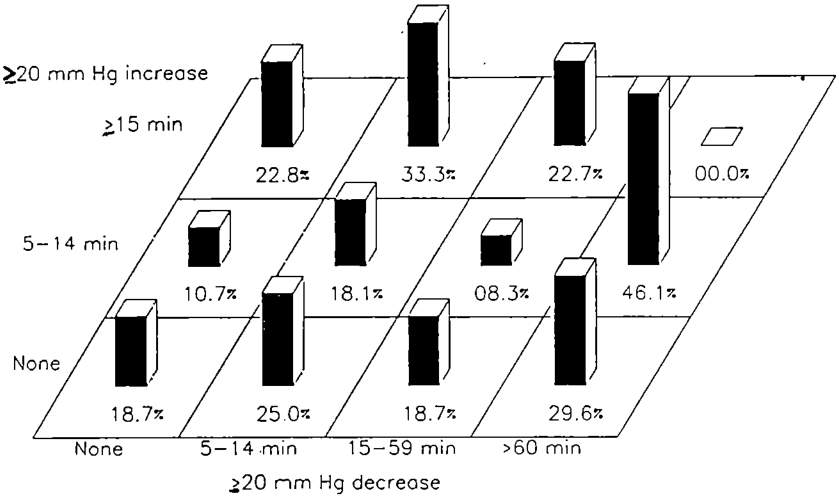


FIG. 1. Postoperative complications according to the duration of ≥20-mmHg intraoperative changes in MAP.

Number of patients per group			
35	18	22	14
28	11	24	13
32	8	32	27

of postoperative complications ($p < 0.02$), taking other covariates into account, and had the highest likelihood ratio. It should be noted, however, that only eight patients had increases lasting more than 1 hour.

Figure 1 shows the complication rates according to the duration of ≥20-mmHg changes, with the duration of decreases plotted on the x axis and the duration of increases plotted on the y axis. The height of the bars represents the percentage of patients in each group with cardiac or renal complications. Patients with 60 minutes or more of decreases had increased complication rates. Complications also were increased rates among patients who had both decreases and increases in MAP. When different durations were analyzed (excluding those with either ≥1 hour of increases or ≥1 hour of decreases), the complication rates were significantly increased among patients with more than 15 minutes of ≥20-mmHg increases and 5 to 59 minutes of ≥20-mmHg decreases ($p < 0.04$). In total 29% of 85 patients in these two high-risk groups had postoperative cardiac or renal complications, while 17% of the 170 patients without either of these hemodynamic patterns had complications.

Because preoperative cardiac disease was an important predictor of postoperative complications, patients were stratified accordingly in Figure 2. To preserve adequate numbers in the strata, in this figure patients with no increases and those with less than 14 minutes of increases were grouped together; patients with 5 to 29 and 30 to 59 minutes of decreases also were grouped together. Among patients without cardiac disease, 24% of those in either of the high-risk groups had complications compared to 13% of those not in either high-risk group. Among those with cardiac disease, 45% of those in the high-risk groups had complications compared to 28% of those in neither group.

Together these two high-risk hemodynamic patterns had a 46% sensitivity and a 70% specificity rate; the positive predictive value was 29% and the negative predictive value was 83%.

Changes in Intraoperative MAP: 20 mmHg and 40 mmHg

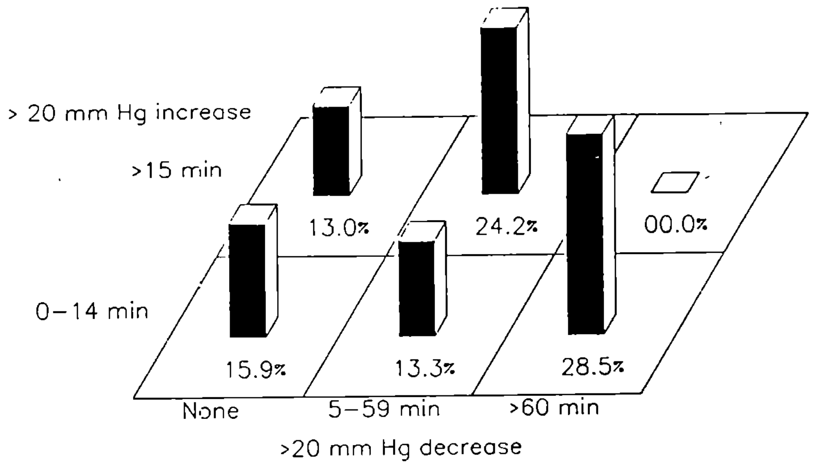
To address the issue of whether the magnitude of the changes was important, a cutoff point of ≥40 mmHg for increases or decreases in intraoperative MAP also was evaluated. Among the patients who had any ≥40-mmHg increase in intraoperative MAP, the complication rate was 22% (*versus* 21% with no increase). Figure 3a shows the complication rates for those with ≥40-mmHg increases according to the duration of ≥20-mmHg increases. When logistic regression was used to assess the importance of any ≥40-mmHg increases relative to ≥20-mmHg increases, the ≥40-mmHg increases were not a significant predictor. It should be noted, however, that two thirds (31 of 46) of the patients developed such ≥40-mmHg increases in the setting of more than 15 minutes of ≥20-mmHg increases.

Among the patients who had ≥40-mmHg decreases in intraoperative MAP, the complication rate was 30% (*versus* 19% with no such decrease). However, as shown in Figure 3b and confirmed by logistic regression, when the duration of the ≥20-mmHg decreases was accounted for, patients with ≥40-mmHg decreases did not have increased complications. It should be noted that 57% (26 of 46) of the ≥40-mmHg decreases occurred in patients who sustained more than 1 hour of ≥20-mmHg decreases in MAP.

Therefore patients who had 40-mmHg changes in MAP did not have significantly greater complication rates once the duration of the 20-mmHg changes were taken into account. However it must be noted that ≥40-mmHg

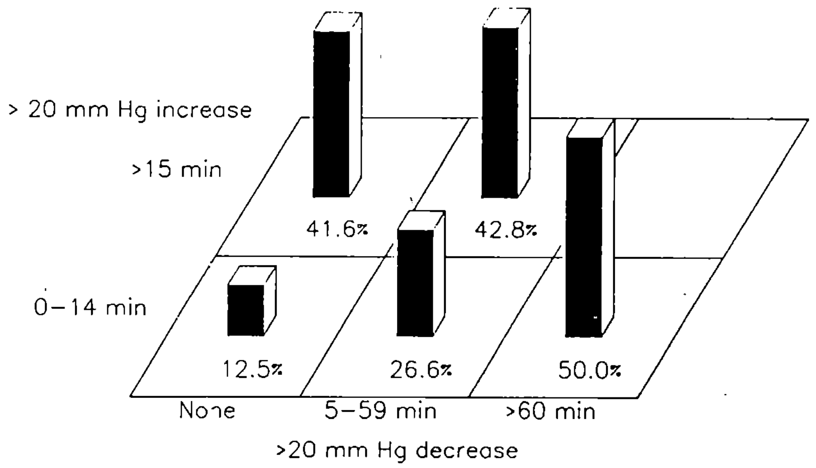
a. No cardiac disease

Number of patients per group		
22	32	4
42	55	27



b. Cardiac disease

Number of patients per group		
12	9	0
18	20	13



c. All patients

Number of patients per group		
34	41	40
60	75	0

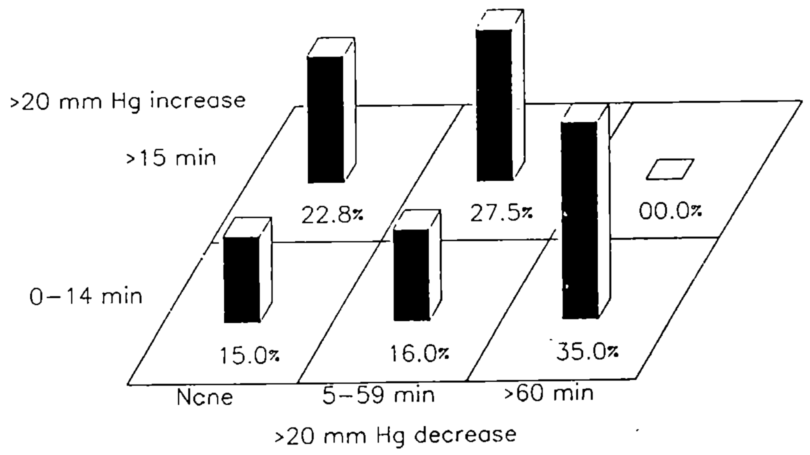
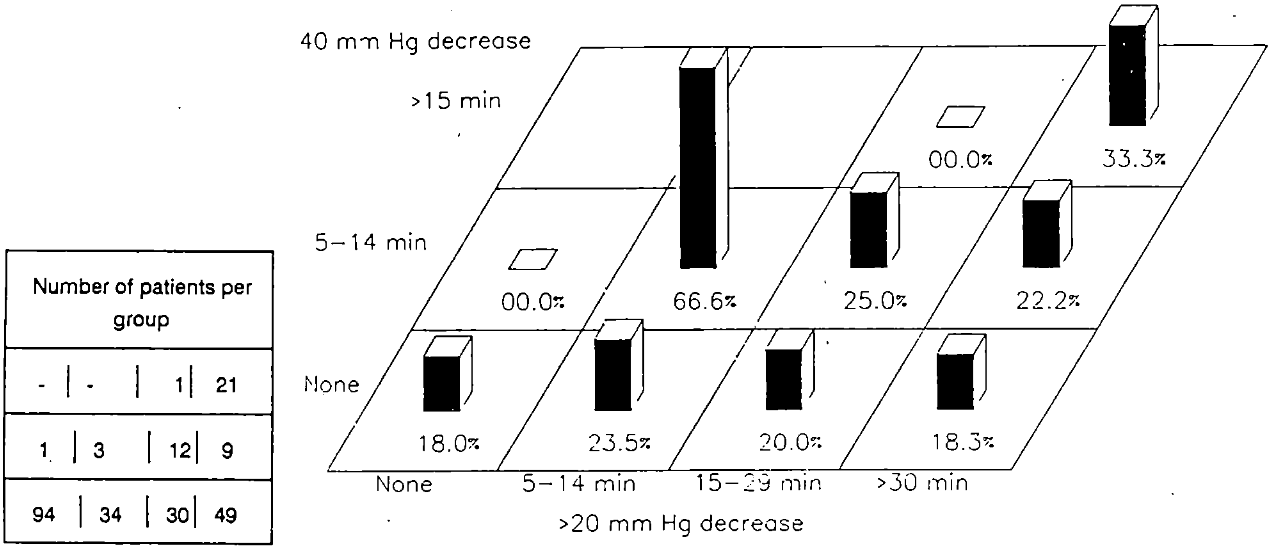


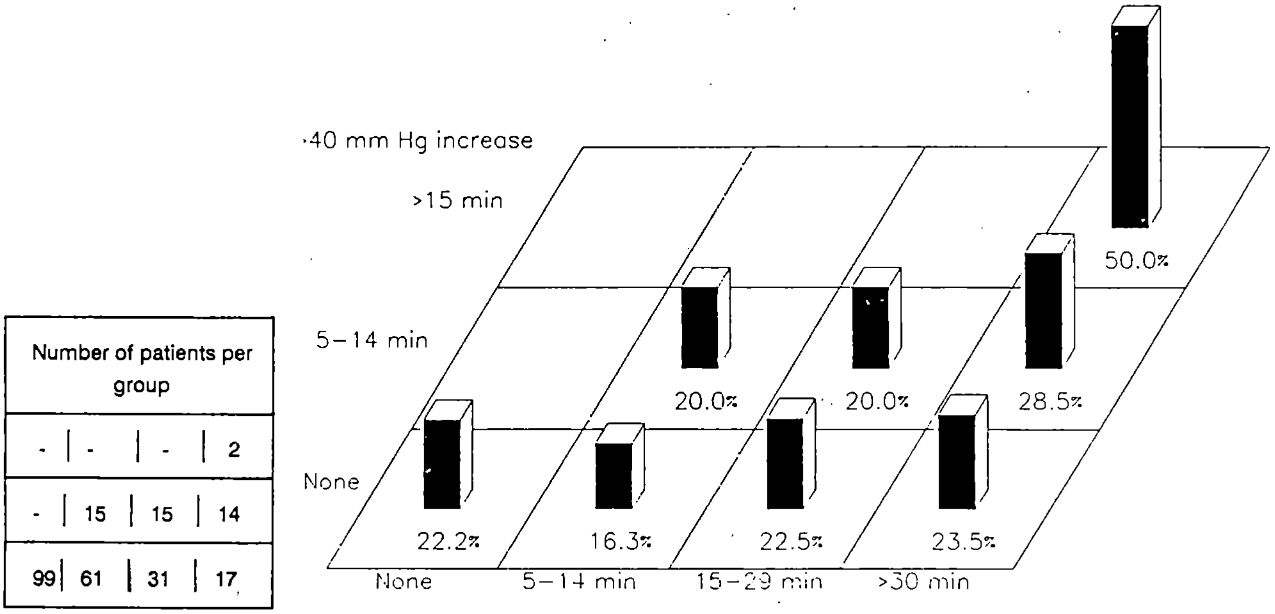
FIG. 2. Postoperative complications according to the duration of ≥20-mmHg intraoperative changes in MAP.

a. 20 mm Hg decrease vs 40 mm Hg decreases



Number of patients per group			
-	-	1	21
1	3	12	9
94	34	30	49

b. 20 mm Hg increases vs 40 mm Hg increases



Number of patients per group			
-	-	-	2
-	15	15	14
99	61	31	17

FIGS. 3a and b. Postoperative complications according to duration and magnitude of intraoperative increases in MAP.

changes usually occurred in the setting of more than 1 hour of ≥20-mmHg changes.

Changes in Intraoperative MAP: 20%, 33%, 40%, and 50%

Because 20% changes in MAP have been used to characterize the intraoperative course,[10] 20% changes were evaluated in relation to 20-mmHg changes. When the patients with 20% increases in MAP were compared to those with 20-mmHg increases above preoperative MAP, 87% of the patients were identically classified according to the magnitude and duration of the changes ($R^2 = 0.74$). Similarly when decreases of 20 mmHg were compared to decreases of 20%, 85% of the patients had changes of identical duration ($R^2 = 0.94$). In short the results of analyzing the intraoperative patterns using 20% changes in MAP were virtually identical to using 20 mmHg. As a result the sensitivity, specificity, and predictive value of 20% changes in MAP were nearly identical to those for 20-mmHg changes. Similarly 40% changes and 40-mmHg changes resulted in nearly identical classification of patients.

Because a 50% decrease in intraoperative MAP of any duration or a 33% decrease for more than 10 minutes have been used[4] to characterize the intraoperative course, these definitions also were evaluated. In this study there was no difference in the complication rates of patients with and without a 50% decrease in MAP (21% of the 14 patients with such a decrease and 21% of the 240 patients without). Consequently the sensitivity of a 50% decrease in MAP was low (5%), and the specificity was high (95%), while the positive predictive value was 21%. Among the 44 patients with a 33% decrease for 10 minutes or more, 25% had complications (*versus* 21% without a 33% decrease). A 33% decrease had a sensitivity rate of 24%, and a specificity rate of 83%, with a positive predictive value of 26%. In both instances of these larger-magnitude percentage changes, the sensitivity was relatively low and the specificity was relatively high in predicting complications. Logistic regression confirmed that neither was a significant predictor once other covariates were taken into account.

Changes in Intraoperative MAP: Mean difference in Intraoperative MAP

With modern monitoring devices that can record intraoperative blood pressure for computer analysis, the simplest method to assess the difference between preoperative MAPs and intraoperative MAPs would be to calculate the mean difference between the preoperative and intraoperative MAPs for the whole operation. A 20-mmHg mean difference in intraoperative MAPs in relation to the baseline preoperative MAPs was evaluated. Figure 4 shows the mean differences in intraoperative MAP plotted *versus* the duration of ≥20-mmHg increases and the duration of ≥20-mmHg decreases. Figure 4a shows the 10 patients who had a mean intraoperative MAP that was ≥20 mmHg higher than their preoperative MAPs; most of these patients had more than 15 minutes of ≥20-mmHg increases in MAP. Figure 4c shows the 24 patients who had a mean intraoperative MAP that was ≥20 mmHg less than their usual mean; these patients had prolonged 20-mmHg decreases. This was as expected.

However the methodologic difficulty with using mean difference is shown in Figure 4b. In total 220 patients had a mean intraoperative MAP that was within 20 mmHg of their usual MAP. Use of a mean difference would have missed the increased complication rate in many patients who had more than 1 hour of ≥20-mmHg decreases and in many patients who had more than 15 minutes of ≥20-mmHg increases and ≥20-mmHg decreases in MAP. Logistic regression confirmed that the mean difference from preoperative levels was not a significant predictor of complications. While simpler to use, the mean difference from preoperative MAPs would have obscured the hemodynamic pattern in those 66 patients who had both important intraoperative increases and decreases in MAP.

Mean Intraoperative MAP Regardless of Preoperative MAP

Another method of evaluating the intraoperative course is to assess the mean intraoperative blood pressures without regard to preoperative values.[14] For example 9% of the patients had overall mean intraoperative MAPs less than 80 mmHg; 43% had MAPs between 80 and 94 mmHg; 30% had MAPs between 95 and 109 mmHg; and 14% had MAPs ≥105 mmHg. Simple logistic regression suggested that the complication rate was increased when the MAP was less than 80 mmHg.

Forty-two per cent of patients with overall mean MAPs less than 80 mmHg had complications compared to 19% of those with overall mean MAPs more than 80 mmHg. However, as shown in Figure 5, the complication rates were not increased significantly unless the mean MAP, less than 80 mmHg, represented more than 1 hour of MAPs that were ≥20 mmHg less than preoperative baseline values. The sensitivity of overall intraoperative mean MAPs less than 80 mmHg in predicting complications was 18%, the specificity was 93%, and the positive predictive value was 41%. Logistic regression confirmed that overall mean intraoperative MAP was not a significant predictor of postoperative complications once the other covariates were taken into account.

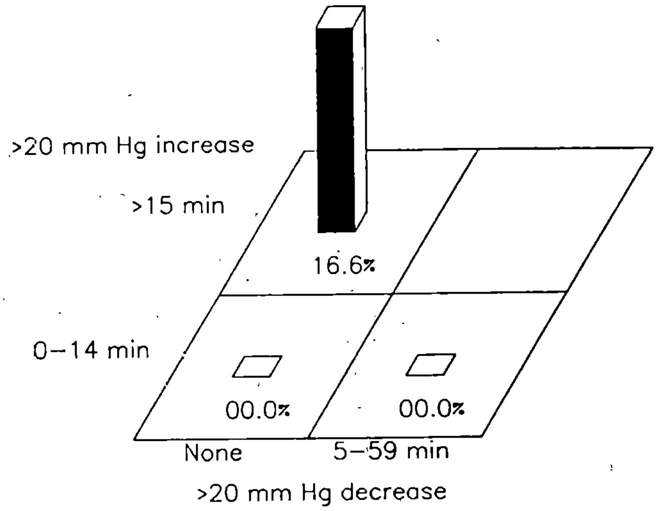
Absolute Intraoperative MAPs Regardless of Preoperative MAP: Less than 70 mmHg or More than 120 mmHg

Another alternative for evaluating intraoperative pressures has been to evaluate a specific MAP level as a

Mean difference in intra-operative MAP

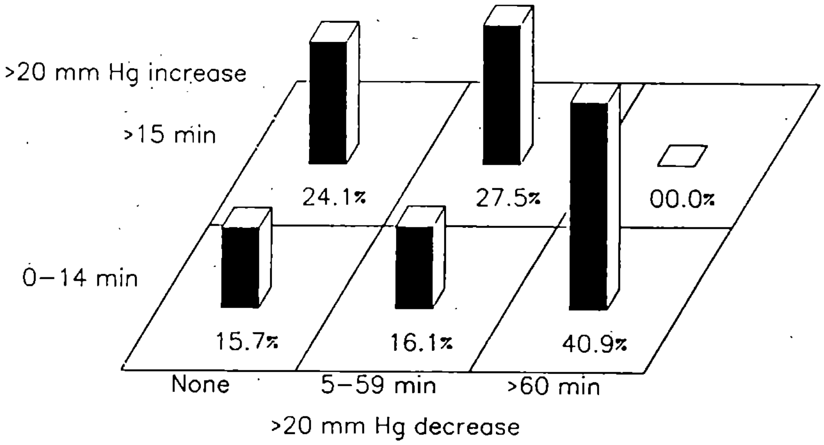
a. ≥ 20 mm Hg above baseline

Number of patients per group	
6	-
3	1



b. Within 20 mm of baseline

Number of patients per group		
29	40	4
57	68	22



c. >20 min below baseline

Number of patient per group	
6	18

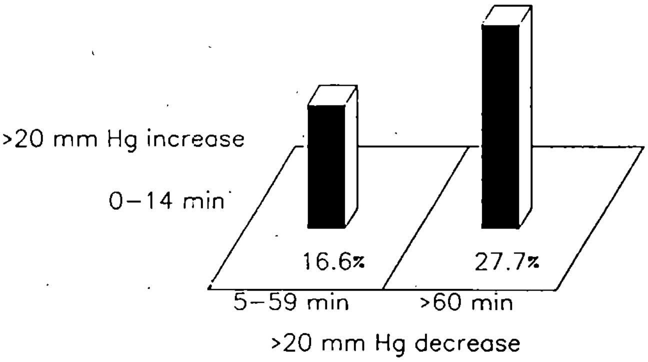


FIG. 4a–c. Postoperative complications according to the duration of 20-mmHg changes in MAP and the mean difference in MAP in intraoperative MAP in relation to baseline.

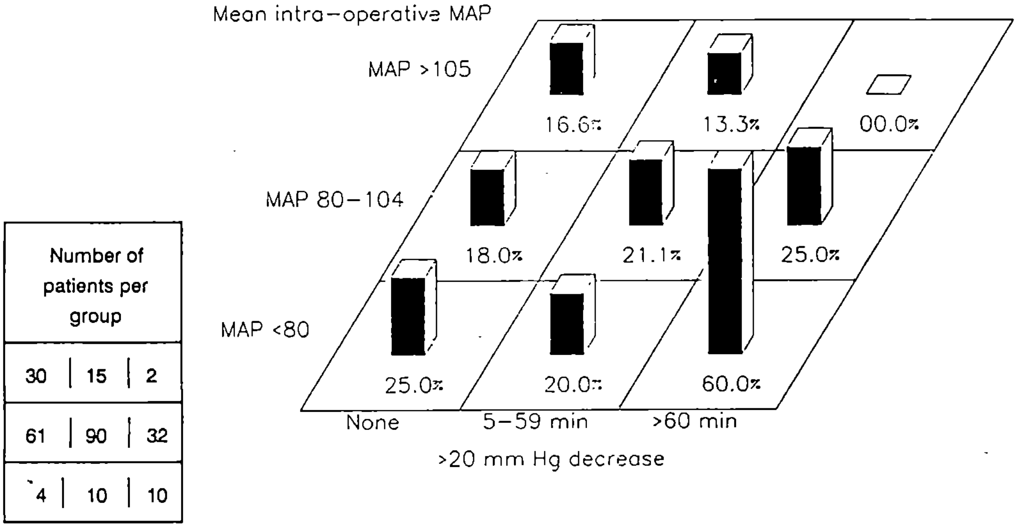


FIG. 5. Postoperative complications according to the duration of 20-mmHg change in MAP and the mean intraoperative MAP, regardless of preoperative MAP.

threshold level below or above which complications are believed to increase. For example 70 to 80 mmHg has been used as a critical threshold for intraoperative MAPs.[28,29]

Of those with more than 15 minutes of MAPs ≤70 mmHg, 31% had complications *versus* 20% of patients with less than 15 minutes. In comparison 11% of those without MAPs ≤70 mmHg had complications. The sensitivity of a MAP less than 70 mmHg for more than 10 minutes was 30% and the specificity was 82%. Figure 6 shows the complication rates according to whether patients had intraoperative pressures of ≤70 mmHg. Within the MAP strata for 20-mmHg changes, an intraoperative MAP of ≤70 mmHg made a noticeable difference only among those patients who had decreases in MAP of ≥20 mmHg for more than 1 hour: in this group 15% of those with less than 14 minutes and 33% of the patients with more than 15 minutes of MAPs ≤70 mmHg had complications, almost two to four times the rate among patients without MAPs ≤70 mmHg. Logistic regression revealed that patients who had MAPs less than 70 mmHg did not have increased complications on the whole; within the strata of patients with 5 to 59 minutes of ≥20-mmHg decreases, an absolute MAP less than 70 mmHg did not achieve significance ($p = 0.12$).

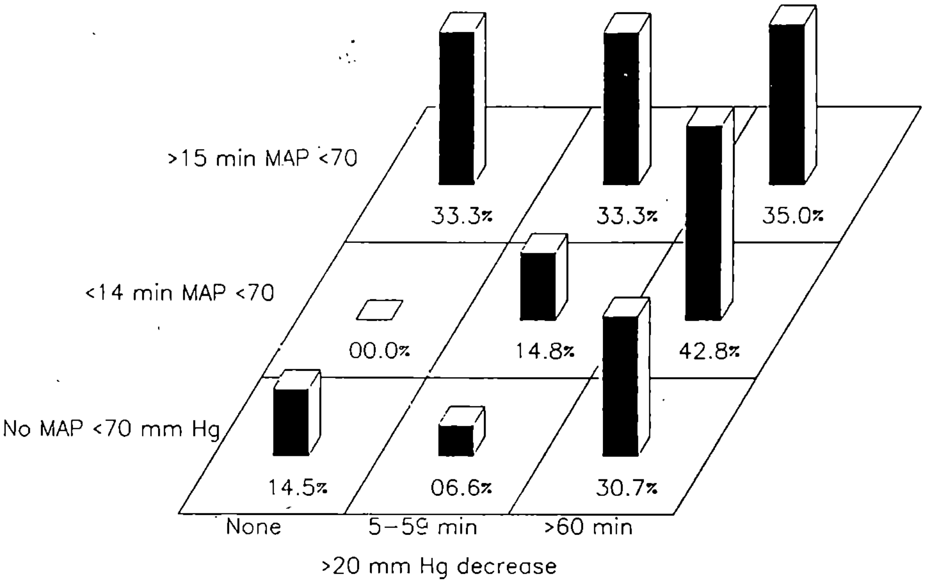
Elevated pressures also were evaluated. For example patients who had intraoperative MAPs ≥120 mmHg for varying durations were evaluated. Patients without such pressures had a 25% complication rate; those with less than 10 minutes had a 19% rate, and those with more than 10 minutes had 22% complication rate. The sensitivity of 120 mmHg for more than 10 minutes was 31%, the specificity was 69%, and the positive predictive value was 21%. Logistic regression confirmed that the use of 120 mmHg did not add prognostic information.

Discussion

The methods used by different studies to characterize the intraoperative hemodynamics vary widely, which impairs our ability to compare the results of the studies. For example percentage changes in the systolic pressure or MAP or absolute changes in intraoperative pressure have been used to define intraoperative hypertension or hypotension.[1-10] This is the first paper to systematically explore the issue of how intraoperative changes in blood pressure should be measured to optimally predict postoperative complications. The purpose of this study was to provide a framework and an initial starting point to standardize the method by which we characterize the intraoperative hemodynamic course. Clearly these findings must be tested and confirmed or refuted by other investigators.

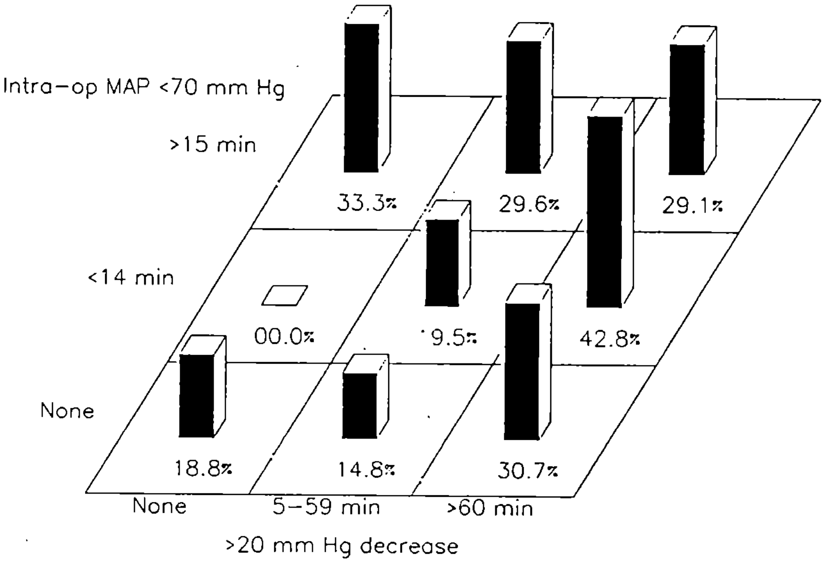
The true-positive rate or sensitivity is the percentage of patients with cardiac or renal complications who had the specified changes in intraoperative blood pressure; if all patients who had complications had the specified changes, the sensitivity would be 100%. The false-positive rate is the percentage of patients without cardiac or renal complications who had the specified changes in intraoperative blood pressure. If none of the patients without the specified changes in blood pressure had complications, the false-positive rate would be 0%. An optimal definition of intraoperative changes in blood pressure in identifying patients with postoperative complications would have a true-positive rate of 100% and a false-positive rate of 0%. In Figure 7 the true-positive rate for identifying patients with complications is plotted against the false-positive rate. The points on the graph represent the true-positive and false-positive rates for different definitions of intraoperative changes in blood pressure. Because none achieve the ideal

a. ≥ 20 mm Hg increase = 0 -14 min



Number of patients per group		
3	18	20
2	27	7
55	30	13

b. ≥ 20 mm Hg increase = ≥ 15



Number of patients per group		
3	27	24
7	41	32
85	47	13

FIG. 6a and b. Postoperative complications according to duration of 20-mmHg changes in MAP and the duration of intraoperative MAP ≤70 mmHg.

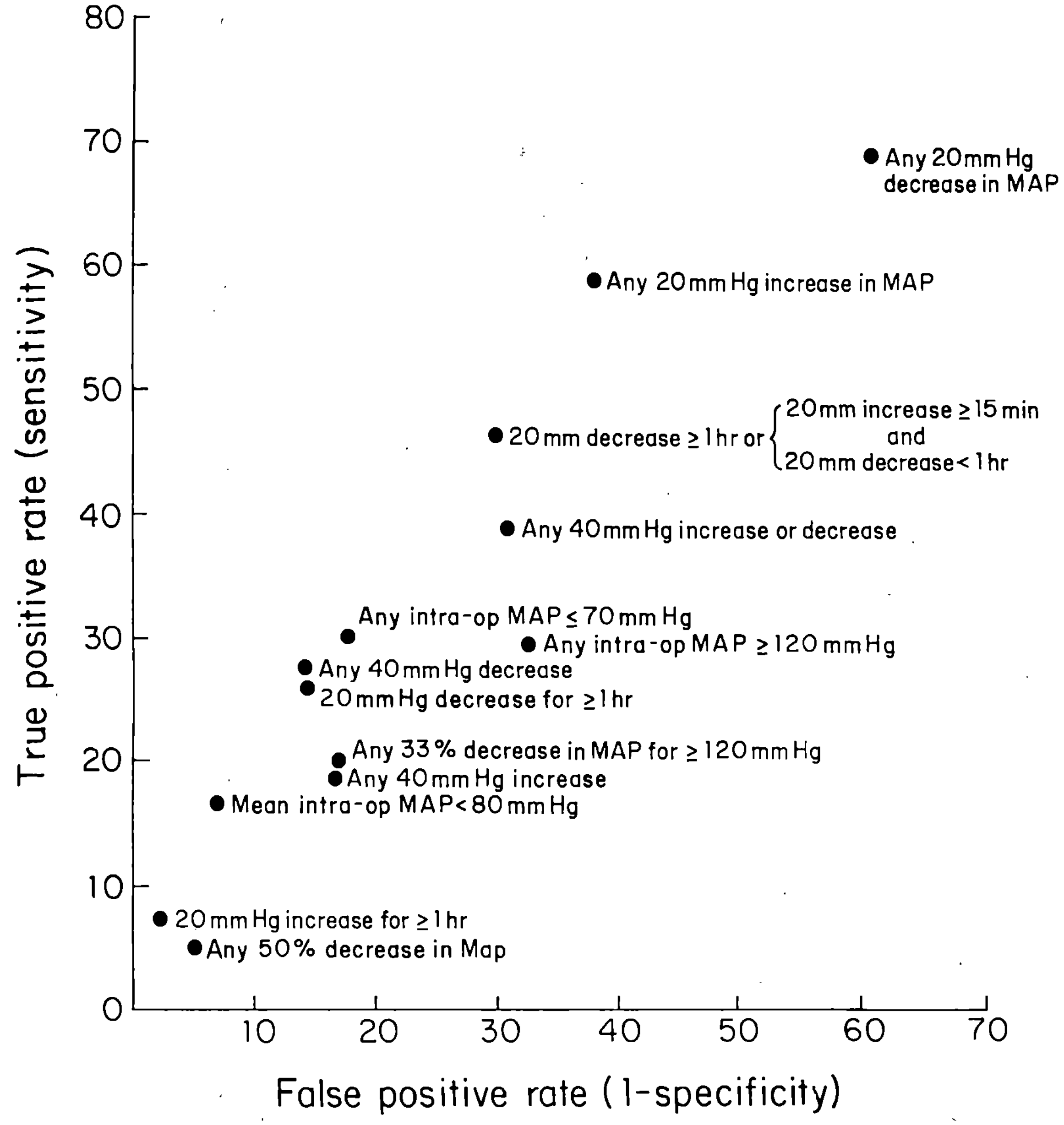


FIG. 7. Receiver operating characteristic curve for different definitions of intraoperative hypotension and hypertension.

of 100% true positive and 0% false positive, the optimal definition is that which maximizes the true-positive while minimizing the false-positive rate. Generally the optimal cutoff is delineated by the point with highest true-positive value before the points begin to curve to the right. In this figure the 20-mmHg differences were the optimal points.

There were several basic findings. First it is important to consider the intraoperative MAPs in relation to the patient's preoperative blood pressure. Strategies that examined absolute intraoperative MAPS, whether the overall MAP or a given threshold value, without reference to the patient's preoperative pressures had a much lower predictive ability than when the changes from preoperative MAPs to intraoperative MAPs were evaluated. Nonetheless, when intraoperative MAPs decreased to less than 70 mmHg, complication rates increased, although the differences were not significant.

Second the use of mean difference in intraoperative pressures from preoperative levels would hide the risk in patients who had intraoperative hypotension and hypertension.

Third patients with greater intraoperative changes in MAP (*i.e.*, more than 40 mmHg) did not have higher complication rates once the duration of the 20-mmHg or

20% changes were taken into account. However most of the larger changes occurred in the setting of ≥60 minutes of ≥20-mmHg decreases or ≥15 minutes of ≥20-mmHg increases.

Fourth two intraoperative hemodynamic patterns were associated with significantly increased postoperative cardiac and renal complications: (1) ≥20-mmHg decreases lasting more than 1 hour, and (2) ≥20-mmHg increases lasting 15 minutes or more and those with decreases of more than 5 minutes but less than 1 hour. The results were nearly identical if changes were defined as 20 mmHg or 20%; in most circumstances the use of 20-mmHg changes, which is much simpler to calculate, may be preferable.

While 20 mmHg may seem like a relatively minor change in intraoperative MAP, this magnitude of change had been hypothesized to be important at the beginning of the study. The reasons for the choice of this cutoff arise from the physiology of autoregulation of regional circulations[28,30] and the impact of anesthesia and surgery on autoregulation.[31] In the coronary and renal circulations, for example, autoregulation preserves perfusion at relatively constant levels despite changes in the systemic pressure within the upper and lower limits for autoregulation.[28,30,31] Below the lower autoregulatory limit, blood flow suddenly decreases, resulting in ischemia; above the upper limit, blood flow suddenly more than doubles, resulting in a local hypermia.[28,30,32,33] Therefore, in coronary and renal circulations, autoregulation preserves perfusion when systemic pressures are within 20 to 30 mmHg of the patient's usual systemic pressure.[30,32,33] The absolute autoregulatory limits are altered in hypertensive patients, partly as a result of structural changes in the vessel wall, and generally are higher and narrower than in normotensive patients.[34] Nonetheless, while the actual limits change, the autoregulatory range remains about 20 to 30 mmHg around the patient's usual MAP. Narrowing of the coronary arteries also may increase the lower limit of autoregulation because the ability to vasodilate in response to increased demands is structurally limited. In summary there is a physiologic basis for the selection of the 20-mmHg change from preoperative levels.

The population in this study consisted mainly of hypertensive and diabetic patients. Thus the extent to which these findings can be generalized to normotensive patients cannot be defined precisely. However the severity of hypertension was not a predictor of postoperative cardiac or renal complications. Diabetes *per se* was a risk factor only for postoperative CHF, and not for renal or ischemic complications. In Goldman's study 29% of the patients undergoing elective noncardiac surgery were hypertensive.[35] In the worst case, this study would have absolutely no applicability to normotensive patients but would apply to the 25% to 35% of patients undergoing elective noncardiac surgery who have hypertension. However it is likely that the sensitivity and specificity of the 20-mmHg changes would be similar in the hypertensive and normotensive population, but that the predictive values would change substantially in a lower-risk population with a lower complication rate.

In this study 25% to 30% of the eligible patients were enrolled. In a previous study of randomized trials, an average of 50% of the patients who met the eligibility criteria were entered into the trials.[36] The critical issue for the validity of the study is the extent to which the results in these patients represented all eligible hypertensive and diabetic patients. It might be helpful to compare the postoperative complications in the two groups; however the surveillance strategy that we used for study patients was more extensive than that used in routine patient care and undoubtedly led to the detection of more postoperative complications in the study group than in patients who were not enrolled. Therefore a comparison of the outcomes may not be as helpful as it appears.

In this paper MAPs were evaluated in relation to postoperative complications. Systolic and diastolic pressures were not evaluated separately, nor were they compared to MAP. Consequently no inferences can be made about the value of the use of the MAP in contrast to systolic/diastolic pressures.

Clearly the issue of how to define optimally intraoperative hemodynamic patterns that place patients at risk for postoperative complications requires further study. The specific results of this study may be confirmed, refuted, or modified by subsequent investigations, but we hope the analytic framework will be useful to others who are faced with the problem of trying to characterize intraoperative hemodynamics.

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Results of a Multicenter Trial Comparing Imipenem/Cilastatin to Tobramycin/Clindamycin for Intra-abdominal Infections

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We designed a multicenter study to compare tobramycin/clindamycin to imipenem/cilastatin for intra-abdominal infections. We included the Acute Physiology and Chronic Health Evaluation (APACHE II) index of severity and excluded patients without established infection. Two hundred ninety patients were enrolled, of whom 162 were evaluable. Using logistic regression to analyze both outcome at the abdominal site of infection and outcome as mortality, we found a significant correlation for both with APACHE II score ($p < 0.0001$ for both). Next we analyzed the residual effect of treatment assignment and found a significant improvement in outcome for imipenem/cilastatin-treated patients ($p = 0.043$). The differences in outcome were explained by a higher failure rate for patients with gram-negative organisms for tobramycin/clindamycin-treated patients ($p = 0.018$). This was reflected in a significantly higher incidence of fasciitis requiring reoperation and prosthetic fascial replacement. Maximum peak tobramycin levels were analyzed for 63 tobramycin/clindamycin patients harboring gram-negative organisms. For failures the maximum peak was 6.4 ± 1.9 µg/mL, and time to maximum peak was 4.6 ± 5.2 days. For successes the maximum peak was 6.1 ± 1.7 µg/mL, occurring at 3.8 ± 2.6 days. This study supports inclusion of severity scoring in statistical analyses of outcome results and supports the notion that imipenem/cilastatin therapy improves outcome at the intra-abdominal site of infection as compared to a conventionally prescribed aminoglycoside-based regimen.

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INTRA-ABDOMINAL INFECTIONS harboring a mixed aerobic and anaerobic flora are significant treatment problems. The overriding importance of early operative intervention prevents precise preoperative bacteriologic evaluation; adjunctive antibiotic therapy therefore must be directed toward a broad range of potentially infecting aerobic and anaerobic organisms.[1] The spectrum of antibacterial activity provided by aminoglycosides in combination with clindamycin or metronidazole has been considered ideal for the anticipated flora of intra-abdominal sepsis. The notable antimicrobial properties of aminoglycosides against *Enterobacteriaceae* and *Pseudomonas* include rapid killing of dividing and nondividing organisms, dose-dependent killing, a postantibiotic effect, and infrequent development of resistance with therapy.[2-4] These factors have been accepted as reasons for the preferred use of aminoglycosides for life-threatening gram-negative infections.[5] In line with these perceptions, comparative trials of antibiotic therapy for intra-abdominal infection generally have used aminoglycoside-based regimens as control therapy.[6]

The renal and auditory toxicities of aminoglycosides and the need for serum level monitoring to ensure therapeutic efficacy in the face of concurrent changes in distributive volumes has stimulated the development of less toxic agents with roughly similar gram-negative spectra.[7-9] The fact that some of these newer agents may engender resistance on therapy for *Pseudomonas aeruginosa* and *Enterobacter* species has led to considerable debate as to their appropriate role in clinical practice.[10,11]

A precise definition of the clinical efficacy of antibiotic regimens for intra-abdominal infection has been ham-

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pered by several problems relating to study design.[12] Sample sizes often have been too small to detect significant differences and cases of peritoneal contamination or inflammation from traumatic bowel, acutely perforated gastroduodenal ulcers, appendicitis, and cholecystitis have been included for evaluation in some studies. Patient characteristics such as age, background diseases, and severity of acute illness are of considerable importance in determining outcome but have not been used in analyzing data from controlled trials.[13]

To circumvent these difficulties, we recently proposed stricter enrollment criteria and the use of severity scoring for patients enrolled in therapeutic trials to allow more precision in intergroup comparisons.[14,15] We suggested use of the Acute Physiology and Chronic Health Evaluation (APACHE II) system.[16] This system assesses three elements: (1) an Acute Physiology Score composed of routine hemodynamic, hematologic, blood gas, and serum chemistry data; (2) age; and (3) a chronic health evaluation encompassing diseases such as renal failure requiring maintenance dialysis, cirrhosis, lung or heart disease symptomatic at rest, and immunosuppressive therapy. This system was developed to analyze mortality for patients receiving medical–surgical intensive care and in this setting has been explored and refined.[17–20] We conducted a retrospective study that supported use of this system.[21]

We now report the results of a prospective, randomized multicenter trial intended to examine the utility of the proposed study design in a comparison of an aminoglycoside (tobramycin) plus clindamycin *versus* imipenem/cilastatin. Imipenem is a carbapenem with a spectrum of activity encompassing the gram-positive, facultative gram-negative, and anaerobic organisms encountered in mixed flora intra-abdominal infections.[22,23] This agent shares certain properties with aminoglycosides, including killing of nondividing organisms, a postantibiotic effect, and activity in the presence of B-lactamase–mediated resistance to third-generation cephalosporins.[24–25] Imipenem is supplied with cilastatin. Cilastatin inhibits a renal dipeptidase that otherwise inactivates imipenem by producing an open lactam metabolite.[27] Previously we reported a single-center study comparing imipenem/cilastatin with gentamicin plus clindamycin in which we encountered a high rate of nephrotoxicity and considerable resistance of *P. aeruginosa* to gentamicin.[28] For this reason we chose tobramycin for the current study.

Methods

The study was conducted from February 1, 1985 to December 31, 1986. Elements of this protocol are described elsewhere.[15] The study protocol was approved by the relevant institutional review boards and written informed consent to participate was obtained from all patients.

Patients 18 years of age or older with history and physical findings suggestive of established intra-abdominal infection were eligible for inclusion. Patients not expected to survive 48 hours, receiving maintenance dialysis, or having a history of anaphylactic or urticarial reaction to B-lactam antibiotics were excluded.[29] Patients receiving immunosuppressive therapy for transplantation also were excluded.

Patients were assigned to one of two randomization lists based on APACHE II scores of less than 15 and 15 or more. The protocol allowed patient entry either before operative intervention or after operation if no intraoperative or postoperative antibiotics were administered. Randomization procedures varied for each center in regards to timing of study enrollment in relation to operation. For the Cincinnati, Seattle, and Los Angeles cases, patients were randomized before operation. The patients at McGill were taken to the operating room having received one dose of cefazolin and then randomized following operative confirmation of active infection. Written consent was obtained before randomization.

Imipenem/cilastatin was administered as 500-mg intravenous doses every 6 hours. Tobramycin was given intravenously at 1.5 mg/kg with dosing interval initially adjusted for serum creatinine. The tobramycin dose and interval then were adjusted to achieve target peak levels ≥ 6 μg/mL and trough levels between 1 and 2 μg/mL. Clindamycin was administered intravenously at 600 mg every 6 hours. If the initial cultures revealed gram-positive organisms believed to be resistant to study therapy, the protocol allowed addition of vancomycin. Eleven tobramycin/clindamycin-treated patients received vancomycin beginning 2 or more days after operation while one imipenem/cilastatin patient was so treated.

Complete blood counts, urinalyses, prothrombin and partial thromboplastin times, multichannel chemistries, blood gas analyses, cultures, and disk susceptibility were performed by each center's clinical laboratories.[30] Minimum inhibitory concentrations were determined by agar dilution using the University of Cincinnati Clinical Microbiology Laboratories as the reference center.[31]

Patients were evaluated for outcome of therapy if (1) they were 18 years of age or older and adequate consent was obtained; (2) an intra-abdominal focus of established infection was documented by operative intervention or by a radiographically controlled drainage procedure; (3) cultures of the site of infection were positive for bacteria; (4) nonprotocol antibiotics were not administered after cultures of the intra-abdominal site of infection were obtained unless the patient suffered an adverse reaction, an extra-abdominal infection, or a failure at the abdominal site. Patients undergoing operation within 12 hours of injury for traumatic bowel perforation, within 24 hours for perforations of gastroduodenal ulcers, and patients with simple acute cholecystitis or nonperforated appendicitis were excluded.

Outcome evaluations were performed for (1) the local intra-abdominal infectious process and (2) hospitalization. Patients were considered nonevaluable if they did not survive 48 hours or longer. Patients surviving longer than 48 hours but less than 7 days were considered treatment failures.

Patients were considered treatment successes if the initial course of study-driven therapy and the initial intervention resolved the intra-abdominal infectious process and if no infectious wound complications occurred.[15,21] If more than one intervention was required to cure the patient of his/her intra-abdominal infection and the initial procedure was considered inadequate, the patient was considered nonevaluable. An operation was considered inadequate if all communications between the gastrointestinal tract and the peritoneal cavity were not closed.

Patients who received additional antibiotics for nosocomial infections started 5 or more days from study entry were scored on the day these agents were begun. Patients with evidence of resolved intra-abdominal sepsis at this time and whose subsequent clinical courses were free of recurrent intra-abdominal infection were scored as successes.

Statistical Elements

Previous studies demonstrated a failure rate of approximately 25% with certain aminoglycoside/clindamycin-based regimens.[1] We chose a sample size that would detect a 50% difference in treatment outcome with an α value of 0.05 and β value of 0.20.[32] This gave us a sample size of approximately 90 cases per treatment arm. We expected a nonevaluability rate of 30% and therefore chose a sample size of 300 patients.

Logistic regression analysis of APACHE II scores *versus* failures or deaths was performed using the Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL). Other statistical tests included chi square testing and Student's t test.

Results

Two hundred ninety patients were entered in the trial. One hundred twenty-eight patients were considered to be not evaluable for reasons outlined in Table 1, yielding an exclusion rate of 44%. The most common reason for exclusion was absence of intra-abdominal infection at the initial operative procedure. This group included 17 with nonperforated appendicitis, 32 with small bowel or colonic noninfectious inflammatory or obstructive disease, 5 with acute cholecystitis, 3 with pancreatitis, 5 with suspected postoperative infection, and 10 with no disease found.

The four deaths in patients with no intra-abdominal infection occurred in patients with intestinal strangulation. The average APACHE II score for this group was 27.5. The single death without operative intervention occurred in a patient found to have hemorrhagic pancreatitis. Five deaths occurred within 48 hours of study entry. One patient had clostridial sepsis and died before exploration, and the other four had diffuse peritonitis from enteric sources. The average APACHE II score in this group was 28.4. Two elderly patients with acutely perforated duodenal ulcers died of irreversible shock. One additional patient excluded because of acute renal failure with creatinine of 5.2 on admission to the study died after oper-

TABLE 1. *Reasons for Exclusion of 128 Patients**

Reason	Total	Tobramycin/ Clindamycin	Imipenem/ Cilastatin
Intervention performed but no infection found	72	40 (3)	32 (1)
No intervention performed	18	8	10 (1)
Survival < 48 hours	5	1 (1)	4 (4)
Enteric perforation from trauma <12 hours or from gastroduodenal ulcer <24 hours	20	9 (1)	11 (1)
Medication errors	3	1	2 (1)
Candida infection with no bacterial copathogens	2	1 (1)	1
Nonadmissible infection	4	1	3
Inadequate initial operation	4	—	4 (2)
Total	128	61 (6)	67 (10)

* Numbers in parentheses are deaths.

[1] During operations on two patients to drain peripancreatic abscesses, dehisced Roux-en-Y pancreaticojejunostomies were left in place; during operation to drain an intra-abdominal abscess and resect necrotic fascia, an unrecognized gastric injury occurred that fistulized. A patient was explored for peritonitis and appendectomy performed, but developed severe adult respiratory distress syndrome and at re-exploration a missed duodenal ulcer was found.

TABLE 2. *Demographics of Evaluable Patients*

Demographic	Tobramycin/ Clindamycin	Imipenem/ Cilastatin
Sex (M:F)	49:32	51:30
Age (years)		
<50	23	33
50–59	10	16
60–69	24	13
70–79	17	13
>79	7	6
Malignancy	14	15
Alcoholism	13	13
Malnutrition	9	12
Diabetes	3	2
Cirrhosis	2	6

Definitions used for associated diseases are from reference 23.

ation to treat a perforated colonic diverticulum with peritonitis.

Four patients were considered to have had inadequate operations for infection. In each case the operative procedure failed to close communications between the gastrointestinal tract and the peritoneal cavity. These cases are detailed further in Table 1.

The operative therapy for four otherwise evaluable patients at one institution included insertion of a zipper and daily intensive care unit abdominal cavity irrigations with saline.[33] Three were randomized to imipenem/cilastatin (two successes) and one to tobramycin/clindamycin (failed). All had undergone previous operation for intra-abdominal infection and were entered in this study after re-exploration for peritonitis or multiple abscesses. The imipenem/cilastatin failure developed recurrent sepsis with persisting *Proteus mirabilis*, *P. aeruginosa*, and enterococci. The tobramycin/clindamycin failure died on the eighth study day with continuing sepsis. While there is considerable controversy regarding this procedure,[34,35] these four patients were considered evaluable.

The demographic characteristics of the 162 evaluable patients, 81 randomized to tobramycin/clindamycin and 81 to imipenem/cilastatin, are presented in Table 2. There were no significant differences between the treatment arms by X^2. There were 48 tobramycin/clindamycin patients aged 60 years or older compared to 32 imipenem/cilastatin patients in this age range ($p < 0.05$). To examine the effect of this population age difference, age and acute physiology point scores for each arm were summed. For the tobramycin/clindamycin group, 252 points were awarded for age compared to 221 points for the imipenem/cilastatin group. Six hundred thirty-three points were awarded the tobramycin/clindamycin group for acute physiology score compared to 704 points for the imipenem/cilastatin group. Therefore the age discrepancy was counterbalanced by increased severity scoring. This was confirmed by analysis of cumulative rates of enrollment by APACHE II score, which showed no differences.

Diagnoses Treated

The organ sites responsible for intra-abdominal infection are presented in Table 3, along with APACHE II scoring and overall outcome data. The exclusion from study entry of patients with uncomplicated acute cholecystitis or acutely perforated gastroduodenal ulcers is reflected in the severity of illness of patients remaining in these categories and, particularly in the gastric and duodenal ulcer group, the mortality rate of 38%. Ninety-one infections arose from the distal small bowel or beyond, where a mixed aerobic and anaerobic flora would be anticipated, and 32 patients were enrolled for postoperative infections. The highest failure rates occurred in patients with infections arising from previous operation (38%, 12 of 32 patients), stomach or duodenum (33%, 6 of 18 patients), small bowel (33%, 4 of 12 patients), and colon (28%, 11 of 40 patients).

TABLE 3. *Disease Processes Encountered at the Initial Operation for Infection in Evaluable Patients*

		Tobraymycin/Clindamycin Patients				Imipenem/Cilastatin Patients			
Origin of Infection		No.	APACHE Score Median	Failed	Dead	No.	APACHE Score Median	Failed	Dead
Stomach/Duodenum		10	21	4	5	8	16	2	2
Biliary		12	12	3	1	5	16	0	2
Small Bowel	Abscess	0	0	0	0	1	17	1	0
	Peritonitis	7	7	2	1	4	12	1	1
Appendix	Abscess	10	4	0	0	15	5	0	0
	Peritonitis	6	12	1	0	8	7	0	0
Colon	Abscess	6	15	0	0	5	8	0	0
	Peritonitis	14	13	6	4	15	15	5	3
Postoperative	Abscess	10	14	5	2	12	13	3	2
	Peritonitis	5	11	2	0	5	21	2	1
Other	Abscess	1	16	1	1	2	9	0	0
	Peritonitis	0	0	0	0	1	17	0	0
Total		81		24	14	81		14	11

Bacteriology and Activity of Study Agents

The organisms cultured from intra-abdominal foci are presented in Table 4 and are consistent with previous reports of bacteriology in intra-abdominal infection. The patterns of infection are detailed in Table 5. There were an average of 3.0 isolates per patient in the tobramycin/clindamycin arm and 3.8 in the imipenem/cilastatin arm. Fourteen patients in the tobramycin/clindamycin arm and 11 patients in the imipenem/cilastatin arm had monomicrobial infections, 11 and 7 of which, respectively, were due to gram-negative organisms. Gram-negative organisms were involved in 63 of the infections in patients receiving tobramycin/clindamycin (77%) and in 67 of the infections in patients treated with imipenem/cilastatin (83%). Anaerobes were involved in 52% of the infections.

The *in vitro* susceptibility of these organisms to the study agents is presented in Table 6. Minimum inhibitory concentrations were determined for approximately one half of the encountered organisms and disk susceptibility data were available for the remaining organisms. The resistance of *Escherichia coli* to tobramycin was seen at one center. Of the four patients harboring resistant *E. coli*, three were randomized to imipenem/cilastatin and the fourth was changed to amikacin when sensitivities became available. This patient was considered a treatment failure.

The surprisingly high level of resistance of *Bacteroides fragilis* and other *Bacteroides* species to clindamycin was attributed to organisms from Cincinnati and Seattle. An additional 15 *B. fragilis* organisms underwent disk testing, of which 13 were sensitive and 2 were resistant to clindamycin. Thus of 37 *B. fragilis* encountered in the study, 9 (24%) were resistant to clindamycin. In addition to the 15 *Bacteroides* species tested by minimum inhibitory concentration, 12 were sensitive by disk and 7 were resistant. Persistence of *B. fragilis* was seen in one treatment failure, a patient randomized to imipenem/cilastatin.

TABLE 4. *Organisms Encountered in Intra-abdominal Foci*

Organism	Tobramycin/ Clindamycin (n = 81)	Imipenem/ Cilastatin (n = 81)
Gram-negative aerobic and facultative		
E. coli	49 (5)	43 (4)
Enterobacter spp.	13 (1)	9 (1)
Klebsiella spp.	10 (2)	15 (1)
Pseudomonas a.	8	16 (1)
Proteus spp.	5	5
Serratia m.	2	—
Citrobacter spp.	2 (1)	3
Morganella m.	1	1
Others	1*	5†
Gram-positive aerobic and facultative		
Alpha streptococci	23	18
Enterococci	18 (4)	20 (1)
B. streptococci	8 (1)	9
Staph aureus	4	3
Staph epidermidis	3 (2)	7 (2)
Fungi *Candida* species	6	9
Anaerobic Organisms		
B. fragilis	18 (3)	19 (0)
Other *Bacteroides*	11 (2)	23 (3)
Clostridia spp.	10 (2)	19
Peptococci/strep.	6	6
Fusobacterium spp.	2	8
Lactobacillus	4	5
Eubacterium spp.	4	3 (1)
Others	5 (2)	15
C. albicans	6	9

Parentheses indicate bacteremias.

* *Hafnia* alveoli.

† Hemophilus parainfluenza × 3, *Bacillus* sp, and unidentifiable Lac + GNR. Blood cultures were obtained at the investigators' discretion. From this incomplete survey, 17 tobramycin/clindamycin-treated patients were bacteremic within 72 hours of study entry and 6 of these were polymicrobic. Eleven imipenem/cilastatin-treated patients were bacteremic; three were polymicrobic.

TABLE 5. *Microbiologic Patterns of Encountered Infections*

Pattern	Tobramycin/ Clindamycin (n = 81)	Imipenem/ Cilastatin (n = 81)
Gram-negative facultative rods only	21	14
Gram-negative rods + anaerobes	10	12
Gram-negative rods + gram-positive cocci	16	17
Gram-negative rods + anaerobes + gram-positive cocci	16	24
Total gram-negative rods	63	67
Gram-positive cocci only	9	7
Anaerobes only	2	3
Gram-positive cocci + anaerobes	7	4

Outcome Results

The incidence of treatment failure or death from intra-abdominal infection for this prospective study sample is presented in Figure 1 using the combined data from both treatment arms. There was an increasing incidence of both failure to control the intra-abdominal infection and death from all causes with increasing APACHE II scores.

We performed logistic regression using as outcome parameters either failure or death. APACHE II score was a significant predictor of failure ($X^2 = 10.11$, $p = 0.0015$). Treatment regimen was also a significant predictor for failure with $X^2 = 4.10$, $p = 0.043$ favoring imipenem/cilastatin therapy. The model X^2 was 14.46, $p = 0.0007$. These results were transformed into cumulative failures *versus* APACHE II for display purposes and are presented in Figure 2. Using survival as the predicted variable, only APACHE II was a significant contributor to the predictive model ($X^2 = 19.02$, $p < 0.0001$). The model $X^2 = 26.07$, $p < 0.0001$.

TABLE 6. *Activity of Study Agents Against Facultative Gram-negative Bacteria*

Bacteria	Tobramycin MIC 90	Tobramycin MIC 50	Tobramycin MIC Resistant	Imipenem MIC 90	Imipenem MIC 50	Imipenem MIC Resistant
E. coli (44)	4.0	1.0	5	0.25	0.25	0
Enterobacter (17)	1.0	1.0	0	1.0	0.25	0
Klebsiella (22)	1.0	0.57	0	1.0	0.25	0
Proteus (8)	1.0	0.5	0	4.0	2.0	1
Pseudomonas a. (10)	4.0	2.0	1	2.0	1.0	0
Citrobacter sp. (5)	16.0	4.0	2	0.5	0.25	0
Other gram negative (4)	2.0	1.0	0	4.0	4.0	0
Breakpoints . . . tobramycin, 4	imipenem, 4					

Activity of Study Agents Against Common Anaerobic Bacteria

Bacteria	Clindamycin MIC 90	Clindamycin MIC 50	Clindamycin MIC Resistant	Imipenem MIC 90	Imipenem MIC 50	Imipenem MIC Resistant
B. fragilis (22)	16.0	1.0	7	0.50	0.12	0
Bacteroides sp. (15)	16.0	1.0	7	0.50	0.25	0
Clostridia sp. (9)	4.0	2.0	4	2.0	0.12	0
Enterococci (22)	—	—	—	4.0	1.0	0
Breakpoints . . . clindamycin, 2	imipenem, 4					

MIC, minimum inhibitory concentration.

The bases for failure are presented in Table 7. Thirty-three of the thirty-eight failures were due to persistent or recurrent infection; 13 tobramycin/clindamycin and 8 imipenem/cilastatin patients underwent reoperation and 5 and 3 patients, respectively, died with clinically obvious ongoing intra-abdominal sepsis before reintervention was performed. The notable difference between the treatment arms occurred in the incidence of fasciitis requiring operative debridement and, in all but one, insertion of a prosthetic fascial substitute (7 in the tobramycin/clindamycin arm *versus* 1 in the imipenem/cilastatin arm). This difference was significant ($X^2 = 5.123$, $p < 0.05$).

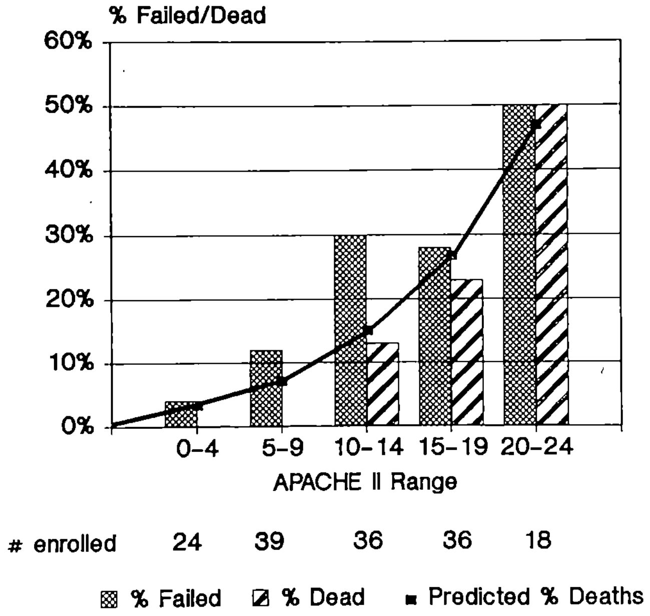

FIG. 1. Depicted are the numbers of patients in each APACHE II range using the combined data from both treatment arms (left axis). APACHE II score was a significant predictor of failure ($X^2 = 10.11$, $p = 0.0015$). APACHE II score was a more significant predictor of death ($X^2 = 19.02$, $p < 0.0001$). Data for predicted deaths were obtained from reference 28.

Because the principal purpose of aminoglycoside therapy is for treatment of facultative gram-negative bacteria, we compared outcome for patients with gram-negative bacteria randomized either to imipenem/cilastatin or to tobramycin plus clindamycin. With this data set, APACHE II score was a significant predictor of failure ($X^2 = 8.95$, $p = 0.0028$). Treatment was also a significant predictor of outcome with an increased success rate following therapy with imipenem/cilastatin ($X^2 = 5.65$, $p = 0.0175$). The model X^2 was 14.26, $p = 0.0008$. These data are presented in Figure 3. All of the statistical power in this study came from differences in outcome of patients with gram-negative infections. There were no differences in outcome for patients infected with gram-positive and/or anaerobic organisms only.

This difference was primarily due to a higher incidence of treatment failure associated with persisting, initially sensitive gram-negative rods in the tobramycin-treated patients (13 of 63 patients) as compared to the imipenem/cilastatin-treated patients (5 of 67 patients; $X^2=5.65$, $p < 0.05$). The failing initially sensitive gram-negative organisms in the tobramycin/clindamycin patients were *E. coli* (7), *Enterobacter* species (5), *Citrobacter freundii* (1), *Hafnia alveoli* (1), and *Morganella morganii* (1). The initially sensitive gram-negative organisms that failed in the

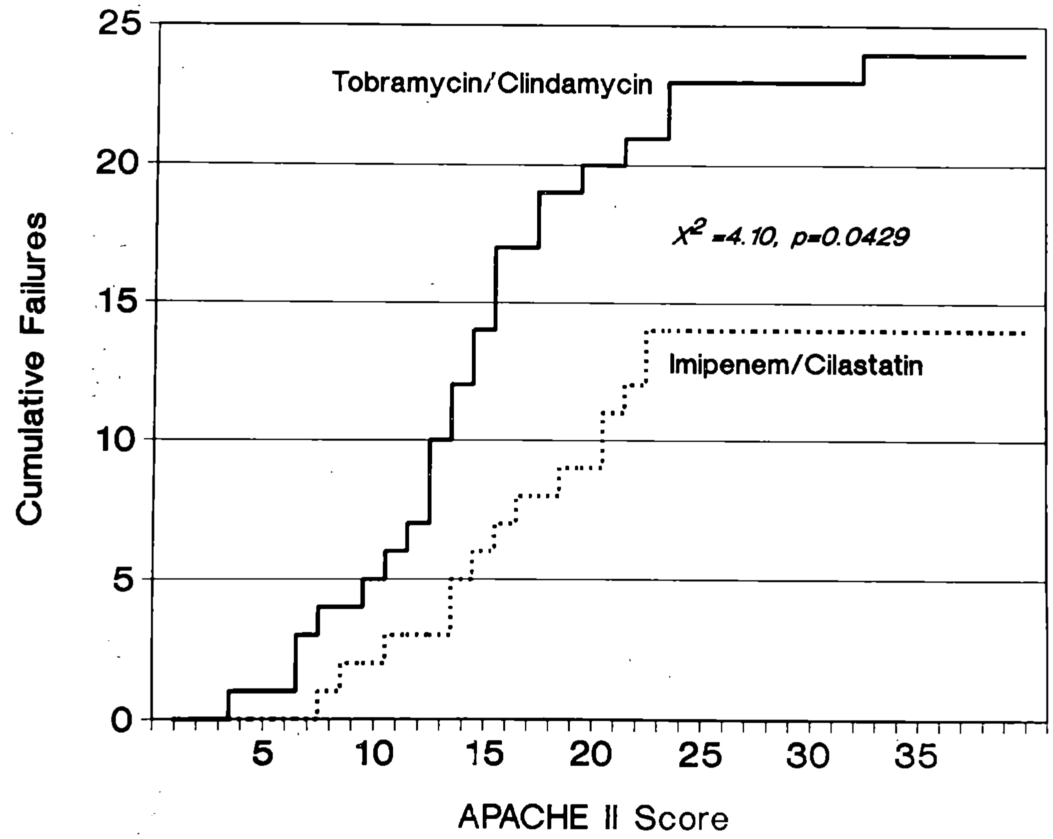

FIG. 2. This figure depicts failure as a function of APACHE II score and antibiotic regimen for all evaluable patients. APACHE II score was a significant predictor of failure ($X^2 = 10.11$, $p = 0.0015$). Treatment regimen was also a significant predictor for failure. There was a residual benefit of imipenem/cilastatin therapy for the entire study population with $X^2 = 4.10$, $p = 0.0429$. The model X^2 was 14.46, $p = 0.0007$.

imipenem/cilastatin-treated patients were *E. coli* (3), *Enterobacter* species (3), *Klebsiella* species (1), *P. mirabilis* (1), and *P. aeruginosa* (1).

We examined the adequacy of aminoglycoside therapy by determining the maximum peak level at any time during therapy for the 63 patients harboring gram-negative organisms. Patients who failed had a maximum peak of 6.38 ± 1.93 μg/mL, and the time from initiation of therapy to the maximum peak was 4.58 ± 5.19 days. For successes (n = 49) the maximum peak was 6.14 ± 1.72 μg/mL, occurring 3.84 ± 2.6 days into therapy. The differences in interval from initiation of therapy to maximum peak were not significant (t = 1.5509).

TABLE 7. *Anatomic and Other Bases for Failure*

Basis for Failure	Tobramycin/ Clindamycin (n = 24)	Imipenem/ Cilastatin (n = 14)
Wound infection	2	3
Recurrent abscess	7†	6
Fasciitis	7	1*
Requiring prosthetic fascial substitute	6	0
Persisting peritonitis	—	2‡
Initially resistant gram-negative organisms	1	—
Expired with ongoing sepsis	5	3
Adverse reaction	3	1§

* X2 = 5.123; $p < 0.05$.

† One tobramycin/clindamycin patient failed with both abscess and fasciitis.

‡ One imipenem/cilastatin patient failed with both peritonitis and fasciitis.

§ One imipenem/cilastatin patient failed with both diarrhea and abscess.

Nosocomial Infections

Infections at other sites were common with both treatment regimens. Of the 81 patients treated with tobramycin/clindamycin, 13 developed nosocomial infections outside of the abdomen. Only three patients had APACHE II scores less than 10 and seven were microbiologic failures at the intra-abdominal site of infection. Four patients developed urinary tract infections, three with *Candida albicans* and one with enterococcus. Eight patients developed pneumonias, seven of which were due to gram-negative organisms (Acinetobacter, Citrobacter, Serratia, *E. coli*, *P. aeruginosa*, and *Xanthomonas maltophilia*). Two patients, including one with a gram-negative pneumonia, developed bacteremias (*S. aureus* and *S. epidermidis*).

The pattern of nosocomial infections was similar in the 81 imipenem/cilastatin-treated patients. Eighteen such patients developed extra-abdominal infections, and only four had an APACHE scores less than 10. Five were treatment failures for their abdominal infections. Eight patients

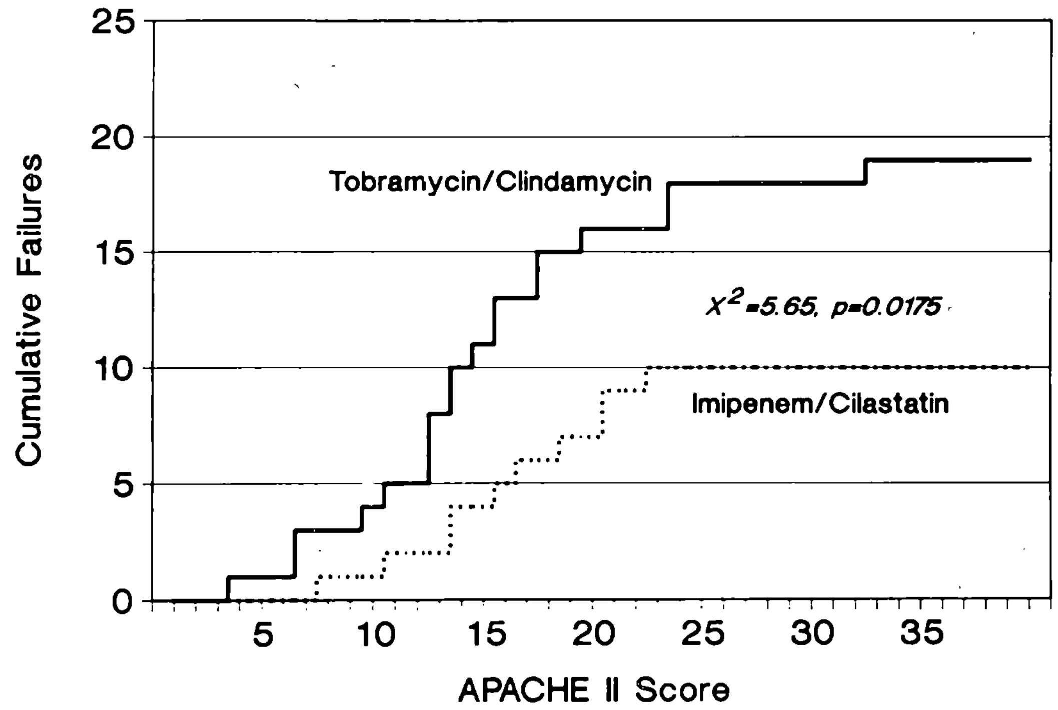

FIG. 3. Depicted is failure as a function of APACHE II score and antibiotic regimen for evaluable patients harboring gram-negative organisms. APACHE II score was again a significant predictor of failure for this patient group with $X^2 = 8.95$, $p = 0.0028$. Treatment was also a significant predictor of outcome with $X^2 = 5.65$, $p = 0.0175$. The model X^2 was 14.26, $p = 0.0008$.

developed urinary tract infections, seven with Candida and one with enterococcus. Nine patients developed gram-negative pneumonias. Four were associated with *P. aeruginosa,* and one each with Acinetobacter and Enterobacter. Three patients developed *X. maltophilia* pneumonia, with one death. One patient developed toxin-positive *Clostridia difficile* diarrhea treated with metronidazole.

Causes of Death

There were 25 deaths among the 162 evaluable patients. The relationship between death and outcome at the abdominal site of infection is presented in Table 8. Seventeen deaths were related to failure to control the initial infection, including 10 tobramycin/clindamycin patients and seven imipenem/cilastatin-treated patients. The clinical details for the eight patients who died following successful treatment of their abdominal infections are presented in Table 8. The mortality rate for patients considered to have received successful therapy for their abdominal infection was 6% (8 of 124 patients), whereas the mortality rate for patients failing therapy was 45% (17 of 38 patients).

Regarding the adverse effects seen, we chose to consider as significant only events that resulted in a change in antibiotic therapy. We noted three patients with suspected

TABLE 8. *Analysis of Deaths*

	Tobramycin/Clindamycin			Imipenem/Cilastatin		
	No.	Average APACHE Score	Survival Time (mean range)	No.	Average APACHE Score	Survival Time (mean range)
Death following successful therapy of intra-abdominal infection	4*	23	17 (11–29)	4†	17	50 (33–85)
Death within 7 days of study entry	5	18	5 (4–7)	1	14	3
Death associated with failure at the abdominal site (>7 days)	5	18	27 (10–42)	6	21	21 (11–40)
Total deaths	14			11		

* 1: unresectable pancreatic carcinoma with superior mesenteric artery involvement; 1: cerebral vascular accident after operation with brain death; 1: unresectable lung carcinoma causing terminal ventilatory failure; 1: cerebral vascular accident and seizures with respiratory arrest and brain death.

† 1: with 2 negative re-explorations, failed to recover and died on day 41; 1: diagnosed after operation with chronic myelogenous leukemia and pancreatic carcinoma; 1: admitted for exacerbation of chronic obstructive pulmonary disease after operation required continuous ventilator support and requested extubation; 1: with cirrhosis, liver failure, ascites developed progressive liver failure with no residual abdominal infection.

aminoglycoside-induced renal failure who required discontinuation of tobramycin; in each case cefotaxime was added. Two patients developed recurrent intra-abdominal infection. One patient treated with imipenem/cilastatin developed a toxin-positive *C. difficile* diarrhea and was treated with metronidazole. Two patients receiving imipenem/cilastatin and one receiving tobramycin/clindamycin experienced seizures and all complications were considered possibly drug related. One nonevaluable tobramycin/clindamycin-treated patient was excluded for orthotopic liver transplantation and received additional antimicrobial therapy. One evaluable patient with a computed tomogram-documented cerebral infarct was continued on imipenem/cilastatin but failed with recurrent abscesses. The third patient experienced seizure on the 12th day of therapy and antibiotic therapy was discontinued.

Discussion

The current study was intended to evaluate a recently proposed design for comparative trials of therapeutic interventions in intra-abdominal infections.[14,15] This design was based on exclusion from study entry of patients with no organisms isolated from the site of infection and exclusion of patients with intra-abdominal contamination or inflammation only (perforated gastroduodenal ulcers operated on within 24 hours, traumatic bowel perforation operated on within 12 hours, simple appendicitis, or cholecystitis). Furthermore either operative or percutaneous drainage procedures were required. These criteria resulted in a study population with demographic characteristics, intra-abdominal diseases, and microbiologic findings consistent with perceptions and previously reported studies of intra-abdominal infections.

We used the APACHE II scoring system as a single numerical descriptor of severity of illness with weighting for age and chronic disease. In a previous study of intra-abdominal infections, we identified the highly significant role of the Acute Physiology Score, the numerically principal element in the APACHE system, in mortality prediction by use of discriminant function analysis.[21] There was a residual effect of age in predicting mortality, an effect only half as powerful as APS. A prospective validation of these results, subsuming age under the more recent APACHE II score, has been reported.[36] Additional findings of these studies were that the degree of localization (abscess *versus* peritonitis) and site of infection, other than appendicitis, did not correlate with outcome independent of the APACHE II score. These observations were confirmed in the present study.

The mortality data from the current study fit well with those previously reported using the APACHE II score (Fig. 1). Comparison of mortality rates with that predicted by APACHE II appears useful in providing assurance that the control arm in the study sample was representative of the class of patients being studied.

The APACHE II system is emerging as a *de facto* standard for describing the severity of illness in studies of intra-abdominal infections.[37] We believe that acceptance of the structure of APACHE II is warranted. This system may be refined as it is applied in settings other than its original use, epidemiologic research on outcome from intensive care. Large sample sizes are required to validate the benefit of added or deleted factors and general use of this system would result in considerable research economies.

APACHE II scoring has been used to group patients into regions of interest. Three scoring regions have been suggested, encompassing low-risk (0 to 10), moderate risk (10 to 20), and high risk (more than 20) patients.[36] This analytic technique obscures the continuous relationship between APACHE II and both failure and mortality and, by decreasing the sizes of comparative groups, reduces the power of the statistical tests applied.

APACHE II scores did not correlate as closely with failure at the local site of infection. While there was a highly significant correlation of APACHE II scores with failure ($X^2 = 10.11$, $p = 0.0015$), failure rates reached a plateau of approximately 30% over an APACHE score range of 10 to 19 and did not increase further until mortality rates increased to 50% (APACHE score range of 20 to 25). At this level of severity early death with documented or suspected on-going intra-abdominal sepsis emerged as a major cause of failure.

We chose to use events at the abdominal site of infection as the primary basis for comparing two antibiotic regimens for intra-abdominal infection. We focused on this endpoint because there is convincing evidence that other accompaniments of infection (*e.g.,* organ failure syndromes) are due to host inflammatory and immunologic responses to lipopolysaccharides and to other products of facultative gram-negative organisms.[38] This response is independent of the presence of live bacteria.

There is no basis for the belief that roughly comparable antibiotic regimens would alter the complex inflammatory pathways triggered early in the disease course by bacterial products. Furthermore we found that 32% of the deaths in this study occurred after cure of the local infection and were due to rapidly progressing malignancy, preterminal chronic cardiac and lung disease, or cirrhosis. Inclusion of these patients as failures of antibiotic therapy would have misstated the role of infection in their deaths.

We compared two antimicrobial regimens with similarly broad activity against facultative gram-negative organisms. The *in vitro* efficacy of both regimens was confirmed by susceptibility testing (Tables 4 and 5). The primary differences between the regimens therefore are related to the pharmacokinetics of the agents and their mechanisms of antimicrobial activity.

The significant improvement in outcome associated with imipenem/cilastatin therapy was due to fewer failures in patients with gram-negative infections (Fig. 3). Our data showed, in turn, that this benefit was due to a decreased incidence of recurrent local infection requiring reintervention and associated with initially infecting gram-negatives susceptible *in vitro* to study therapy. While other forms of analysis have been used, we believe that efficacy of antibiotic therapy is best defined on the basis of the terminal bacteriology at the site of recurrent or persisting infection. We consider the need for reintervention a catastrophic event and we noted a higher mortality rate and a higher incidence of extra-abdominal nosocomial infection in patients requiring reoperation.

Our finding that failures were significantly related to persistence of facultative gram-negative organisms suggests a priority for therapy directed against these bacteria. Aminoglycosides have been considered the agents of choice for serious gram-negative infections. Effectiveness of aminoglycoside therapy has been related to several different parameters derived from time-serum concentration curves. These include the maximum peak plasma level obtained during therapy, the area under the time-concentration curve, and time/24 hours above the minimum inhibitory concentration.[39,40] These variables are interconnected because elevating the peak concentration while maintaining trough concentrations will increase both the area under the time-concentration curve and the time above the MIC. More recently the ratio of the peak level and minimum inhibitory concentration for organisms treated has been suggested as a pharmacokinetic endpoint.[41] We sought to optimize both the maximum peak concentration and area under the curve by specifying target peak levels of 6 or more and trough levels more than 1.

For this report we analyzed outcome of aminoglycoside-treated patients in relation to the maximum peak level obtained. This was not rewarding in that successes and failures achieved similar peak levels at similar intervals into therapy.

The striking finding of this analysis was that the interval from initiation of therapy to achievement of maximum peak levels in patients harboring gram-negative organisms averaged approximately 4 days for successes and failures. This delay is similar to that reported by others in clinical trials.[41] Because efficacy is, in part, related to the timing of therapy, we believe the increased failure rate seen in this study with aminoglycoside therapy was related to this factor. We would speculate that this delay in achieving therapeutic levels accounted for the surprisingly high incidence of fasciitis in the aminoglycoside-treated patients. Persisting gram-negative organisms were recovered from all of these infections.

The other notable microbiologic finding of this study was the lack of correlation between clindamycin resistance and persistence of *B. fragilis* and other *Bacteroides* species at the abdominal site of infection. The clindamycin resistance encountered reflected an increase in MICs to the range of 8 to 16 μg/mL. A previous study analyzing response of *B. fragilis* and other *Bacteroides* species in appendicitis noted no failures with non*fragilis* species, regardless of therapy and clinical success against *B. fragilis* for cefoperazone where the organisms were not susceptible *in vitro* by standard guidelines.[42] These data suggest that *B. fragilis* organisms are more easily killed in non-neutropenic hosts than are gram-negative organisms.

Based on our findings, we prefer imipenem/cilastatin as initial therapy for intra-abdominal infections unless the presence of organisms resistant to imipenem/cilastatin or other B-lactamlike agents is highly suspected (*e.g.*, postoperative intra-abdominal infections in which cultures are available before reintervention). Imipenem/cilastatin was found to be significantly more effective against facultative gram-negative organisms than tobramycin and this finding would recommend its use for intra-abdominal infections other than appendicitis. If aminoglycosides are used in any setting, considerable effort should be devoted to rapid achievement of peak plasma levels six or eight times the measured MIC for the gram-negative organisms being treated.[41]

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Positive Results of Combined Therapy of Surgery and Intraperitoneal Hyperthermic Perfusion for Far-advanced Gastric Cancer

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To evaluate the clinical efficacy of intraperitoneal hyperthermic perfusion (IPHP) for far-advanced gastric cancer, particularly with peritoneal seeding, we investigated the survival times of 59 patients who underwent distal subtotal gastrectomy, total gastrectomy, or total gastrectomy combined with concomitant resection of some of the remaining intra-abdominal organs. In all the 30 patients given IPHP, no cancer cells were present posthyperthermically in the lavage from the Douglas pouch. The 30 patients given IPHP lived longer than the 29 patients not given IPHP ($p = 0.001$), with a 1-year survival rate of 80.4% in the former group compared to 34.2% in the latter. With respect to a comparison of survival time of patients with peritoneal seeding, 7 patients not given IPHP had a 6-month survival rate of 57.1% and did not survive more than 9 months, whereas 20 patients given IPHP had 1- and 2-year survival rates of 78.7% and 45.0%, respectively; here the difference was significant ($p = 0.001$). The IPHP and control groups without peritoneal metastasis included 10 and 22 patients, respectively, and the 1-year survival rates are 85.4% and 45.3%, respectively. The survival rates of the former exceeded those of the latter, with $p = 0.015$ by the generalized Wilcoxon test. Thus this combined therapy offers the promise of extended survival for patients with far-advanced gastric cancer.

THE POOR PROGNOSIS of patients with advanced gastric cancer is caused by peritoneal or hepatic recurrence developed from cancer cells scattered before operation on the peritoneal surface or in the portal vein. Various attempts were made to treat the peritoneal recurrence and/or metastasis; however the results left much to be desired. To prevent peritoneal recurrence after surgical resection, continuous hyperthermic peritoneal perfusion was performed by Koga et al.[1] with good results. We reported that intraperitoneal hyperthermic perfusion (IPHP) led to a remarkable antitumor effect on peritoneal dissemination and peritoneal recurrence from gastric cancer.[2,3] We report here data on 30 far-advanced gastric cancer patients given IPHP, most of whom underwent total gastrectomy. The survival time of these 30 gastric cancer patients given IPHP was compared with data on patients with gastric cancer treated only surgically.

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Subjects and Methods

Patients

From February 1986 IPHP was performed soon after surgery for 30 far-advanced gastric cancer patients, the objective being to treat peritoneal dissemination or to prevent peritoneal recurrence (IPHP group). In contrast 29 patients with far-advanced gastric cancer underwent surgery without IPHP, within the same period of time (control group). The distribution of clinical characteristics in these patients is shown in Table 1.

Intraperitoneal Hyperthermic Perfusion and Antitumor Treatment for the Control Group

Intraperitoneal hyperthermic perfusion was applied, using an apparatus designed for IPHP, as a closed circuit.[2,3] The equipment needed for IPHP (Mera IPH-2, Senkosha, Tokyo, Japan) was inserted into the Douglas pouch and the upper abdominal cavity just before temporary closure of the abdominal wall after the surgical treatment; and in advance of IPHP, the prehyperthermic hypothermia (31 to 32°C) was induced by means of a cooling mat and ice bags (Fig. 1). Successively IPHP, using 3000 to 5000 mL of the perfusate containing 10 μg/mL of mitomycin C

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TABLE 1. *Clinicopathologic Features of Patients*

Factors	IPHP Group (n = 30)	Control Group (n = 29)
Age	52.1 ± 12.6	60.5 ± 10.9
Sex (male/female)	14/16	17/12
TNM classification[5]		
T3	11	18
T4	19	11
N0	4	6
N1	3	4
N2	23	19
Distant metastasis to peritoneum	17 (3)*	7
Organs Involved		
1 organ	8	7
2 organs	11	4
Type of Histology		
Differentiated	5	12
Undifferentiated	25	17
Type of Surgery		
Distal subtotal gastrectomy	5	7
Pancreatico-duodenectomy	1	0
Total gastrectomy	2	9
Total gastrectomy plus splenectomy	3	7
Total gastrectomy, splenectomy plus oophorectomy	5	0
Total gastrectomy, splenectomy plus colectomy and/or partial pancreatectomy	8	6
Total gastrectomy, splenectomy, oophorectomy plus partial pancreatectomy	6	0

* Number in parentheses indicates the patient with cytologically positive results of peritoneal lavage.

(MMC), was carried out for 117 ± 17 minutes, with special attention given to the cardiorespiratory functions and to the rising temperatures in the pulmonary artery.[2–4]

Throughout this IPHP treatment, temperature was measured with six thermometer probes: at the points of inflow and outflow on the abdominal wall, at three spots in the peritoneal cavity, and at the pulmonary artery (Fig. 1). Temperatures in the pulmonary artery were measured by means of an inserted Swan-Ganz catheter and did not exceed 41°C during this treatment. During this IPHP temperatures at the inflow point and in Douglas' pouch were maintained at 45.0 to 47.3°C and 43.6 to 45.1°C, respectively.

On the other hand, for the 29 patients of the control group, 30 to 50 mg of MMC was given intraperitoneally and/or intravenously. There was no statistical difference between both the groups with regard to the doses of MMC.

Statistical Analysis

Survival curves were calculated using the Kaplan–Meier method[6] and survival rates were analyzed using a generalized Wilcoxon test[7] and log-rank test.[8] Background factors were compared between these two groups and chi square test or Student's t test was used to determine the statistical difference.

Results

Clinicopathologic Features of Patients

The mean age in the IPHP group was younger (p = 0.009) than that in the control group (Table 1). As shown in Table 1, of 30 patients given IPHP, 17 proved to have malignant ascitic effusion and 3 of the remaining 13 patients had positive cytologic examination with peritoneal lavage at laparotomy. The remaining 10 patients had serosal invasion of T3. In the IPHP group, total gastrectomy, subtotal gastrectomy, or pancreaticoduodenectomy was performed and 22 of the 30 patients underwent splenectomy, transverse colectomy, right hemicolectomy, partial pancreatectomy, and/or oophorectomy.

The control group included seven patients with malignant ascitic effusion and 18 of the remaining 22 had serosal invasion of T3 (Table 1). Of 29 patients not given IPHP, 16 underwent distal subtotal or total gastrectomy and, the remaining 13 were operated on for total gastrectomy plus splenectomy, colectomy, and/or partial pancreatectomy.

The incidence of peritoneal seeding was higher (p = 0.001) in the IPHP group, compared with the control group, and the ratio of T3 and T4 differed at p = 0.052 between the groups. There were no significant differences between the groups with regard to sex, nodal involvement, and organs involvement. Patients in the IPHP group underwent excision of multiple organs, with a statistical difference at p = 0.028, compared to the control group. In comparison of histology, the IPHP group had a high incidence of 'undifferentiated' tumors (p = 0.036), compared to the control group.

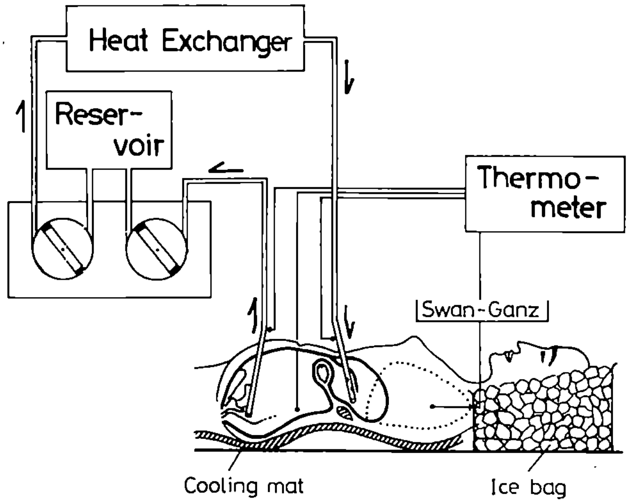

FIG. 1. Schematic drawing of IPHP. Arrows indicate flow direction of the perfusate.

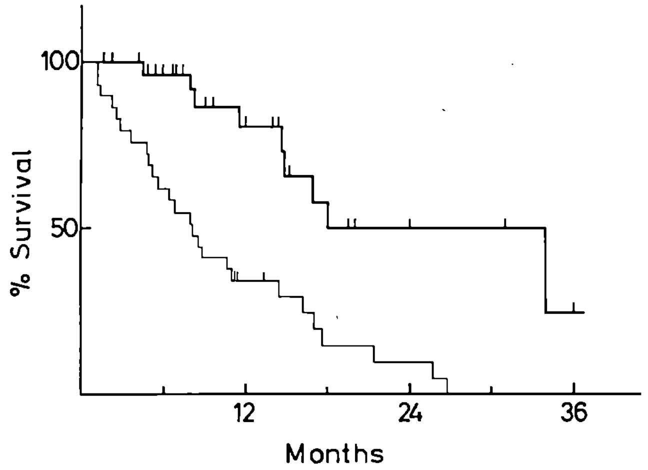

FIG. 2. Survival curves of patients with far-advanced gastric cancer. ——, IPHP group (n = 30); ——, control group (n = 29). The difference between the IPHP and control groups was statistically significant (p = 0.001 by generalized Wilcoxon test and log-rank test).

Antitumor Efficacy

In the 30 patients in the IPHP group, repeated cytologic examinations of the lavage in Douglas' pouch were negative posthyperthermically. With respect to preoperative ascitic effusion of 17 patients with peritoneal seeding in the IPHP group, the ascitic effusion disappeared soon after IPHP.

Survival Rates

The survival rates for the IPHP and control groups are shown in Figure 2. One-, two-, and three-year survival rates for the IPHP group were 80.4%, 49.1%, and 24.5%, respectively, whereas those for the control group were 34.2%, 9.8%, and 0%, respectively. The survival rates for the IPHP group were significantly higher than those for the control group, with a statistical difference of p = 0.001 by the generalized Wilcoxon test and log-rank test (Fig. 2).

The results in terms of 27 patients with peritoneal seeding are shown in Figure 3. Six-, twelve-, and twenty-four-month survival rates of 20 patients with IPHP were 94%, 78.7%, and 45%, respectively, while the 6-month survival rate for 7 patients without IPHP was 57.1%. The survival rates of these 20 patients given IPHP were significantly better than those of the 7 patients treated with surgery alone, with a statistical difference of p = 0.001, as determined by both the generalized Wilcoxon test and log-rank test.

Findings in the cases of 32 patients without peritoneal metastasis are shown in Figure 4. One- and two-year survival rates of 10 patients given IPHP were 85.4% and 56.5%, respectively, while those of 22 patients without IPHP were 45.3% and 12.9%, respectively. Survival rates for the IPHP group were significantly better than those for the control group (p = 0.011 by the log-rank test; p = 0.015 by the generalized Wilcoxon test).

Data on the cause of death are shown in Table 2. The incidences of death due to peritoneal recurrence were 6.7% (2 of 30 patients) in the IPHP group and 51.7% (15 of 29 patients) in the control group, and the difference was statistically significant at p = 0.0001 as determined using the chi square test. With regard to patients with peritoneal seeding at the time of laparotomy, the incidence of death caused by peritoneal dissemination was 10% in the IPHP group and 100% in the control group. With respect to

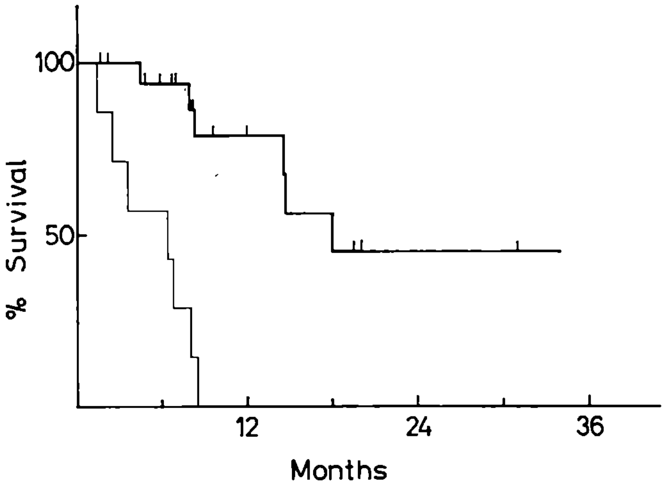

FIG. 3. Survival curves of patients with peritoneal seeding. ——, IPHP group (n = 20); ——, control group (n = 7). There was a significant difference between the survival curves of the IPHP and control groups (p = 0.001 by generalized Wilcoxon test and log-rank test).

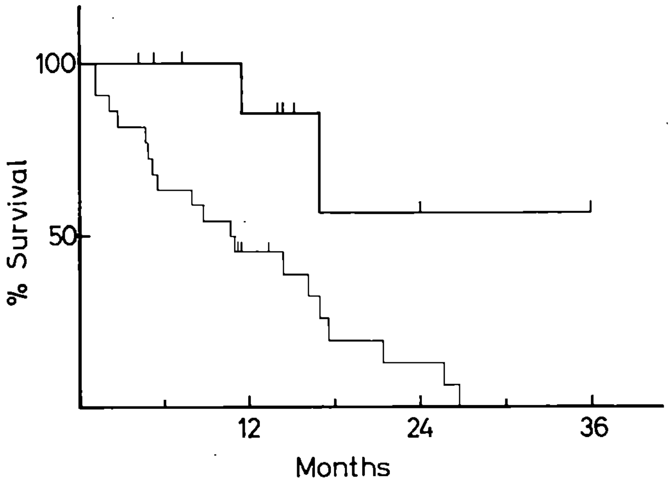

FIG. 4. Survival curves of 32 patients without peritoneal seeding. ——, IPHP group (n = 10); ——, control group (n = 22). There is a statistical difference between the IPHP and control groups (p = 0.015 by generalized Wilcoxon test; p = 0.011 by log-rank test).

TABLE 2. *Outcome of Treatment in Terms of Cause of Death*

	IPHP Group		Control Group	
	Peritoneal Seeding		Peritoneal Seeding	
Cause of Death	(+) n = 20	(−) n = 10	(+) n = 7	(−) n = 22
Peritoneal metastasis	2	0	7	8
Pleural metastasis	2	0	0	0
Intra-abdominal metastatic tumors	2	0	0	5
Hepatic metastasis	0	2	0	3
Others	1	0	0	3
Total	9/30		26/29	

other causes of death, there was no significant difference between the two groups.

Side Effects

Two of the thirty patients given IPHP and one patient in the control group had minor leakage at the anastomosis. The platelet count decreased immediately after IPHP but 7 days later normal ranges were observed. Serum GOT and GPT levels increased considerably after IPHP but at 2 to 3 weeks after normal ranges were recorded. Serum protein dropped during IPHP and reverted to preoperative levels 4 to 7 days later.

Discussion

'Total cell killing' is the objective of treatment for patients with malignant diseases. Even a cure can be achieved for patients with solid malignant tumors with regional nodal involvement when wide local excision with regional lymphadenectomy are carried out. However, when cancer cells invade the blood vessels, the combined treatment of surgery and chemotherapy is indispensable. Intra-arterial cancer chemotherapy has been prescribed for patients with colorectal liver hematogenous metastasis, with considerable success.[9] In many patients with advanced gastric cancer, occult metastatic foci are considered to have already been scattered at the time when surgery is done. To provide added support for the surgery, a clinically available antitumor means aimed at cancer cells in the portal vein and on the serosal surface was devised.

Hyperthermia is particularly effective for human cancers, when applied with chemotherapy.[10] However difficulties are encountered when attempting to apply hyperthermia for lesions of the abdominal cavity with its variously shaped organs. Spratt et al.[11] Koga et al.,[1] and Fujimoto et al.[2,3] performed intraperitoneal hyperthermic chemotherapy to eradicate cancer cells and/or cancerous tumors of small size on the peritoneal surface. An ideal application of hyperthermia is to expose the malignant lesions to a uniform, elevated temperature. The peritoneal surface is heated uniformly with the apparatus we used for IPHP and this IPHP treatment is safe as the temperature of the pulmonary artery is monitored by means of an inserted Swan-Ganz catheter.[2,3]

Yamada et al.[12] reported that the survival rates of 99 patients with an excised primary lesion and malignant effusion and those of 190 patients with an inoperable primary lesion and malignant effusion were 21% and 15% at 6 months after treatment for effusion, respectively, regardless of the intraperitoneal and intravenous administration of antitumor drugs. These results are inferior to the findings of the 7 patients with peritoneal seeding in our control group. Intraperitoneal wide-spread dissemination is probably due to the biologic behavior of gastric cancer cells, which is thought to differ essentially from colorectal cancer, yet to some extent resembles ovarian cancer.

All 7 patients in our control group with peritoneal seeding died within 9 months, while of the IPHP group with 17 patients with peritoneal seeding 2 died of peritoneal recurrence. Free-floating cancer cells and cancer cells on the peritoneal surface are exposed to the high concentration of MMC, in case of IPHP application.[2–4] For larger tumors, however, MMC given intraperitoneally diffuses into the tumoral tissue and MMC concentrations decline after a few layers of cancer cells. A similar phenomenon may be said to occur in case of conduction of heat by blood flow. Thus intraperitoneal tumors of small diameters are severely affected by this IPHP treatment. On the other hand, intraperitoneal large tumors and those that have invaded under or directly under the serosal or peritoneal surface may not be effectively treated by this IPHP with MMC. We reported elsewhere[2] that a patient with peritoneal dissemination underwent this IPHP treatment and at the second operation 5 weeks later, no peritoneal dissemination was found, despite partial residual implantations in the cecum and colon. These partial residual implantations would result from larger tumors and may be the origin of peritoneal recurrence of the two patients in the IPHP group who died.

Our data suggest that to treat patients with peritoneal seeding from gastric cancer, combined surgery and IPHP should be considered. A controlled randomized study remains to be performed. This IPHP treatment led to a favorable outcome for far-advanced gastric cancer patients who had been diagnosed as inoperable. This combined therapy offers promise of extended survival for patients with far-advanced gastric cancer.

Acknowledgment

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Parietal Cell Vagotomy and Dilatation for Peptic Duodenal Stricture

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Gastric outlet obstruction due to peptic duodenal stricture (pyloric stenosis) was treated with parietal cell vagotomy and dilatation of the stricture in 32 patients. Follow-up is in the range of 5 years in 37.4% of the patients, while 6 to 10 years follow-up is available in 62.4% of the patients. At their last follow-up, 74.9% of the patients were in either Visick 1 or 2 clinical status. Recurrence rates have been 3.1% at 1 year, 9.3% at 5 years, and 21.8% after 6 to 10 years follow-up. There has been only one instance (3.1%) of restenosis. Two patients required reoperation because of recurrence and one of them died.

THE FREQUENCY OF peptic duodenal ulcer surgery declined after the introduction of H_2 receptor blockers. However gastric outlet obstruction continues to be a principal indication for surgery.[1] An ideal operation for obstructing peptic duodenal stricture must relieve the obstruction, control the primary ulcer diathesis, and be free of late complications[2]; also it must have a negligible mortality rate and an acceptable rate of postoperative morbidity. Johnston et al.[3] have advocated parietal cell vagotomy and dilatation for the surgical treatment of peptic duodenal stricture. We began performing this procedure in 1979 in unselected patients. Here we report our late results with parietal cell vagotomy and dilatation for peptic duodenal stricture.

Materials and Methods

Parietal cell vagotomy and dilatation was performed in 32 patients with gastric outlet obstruction due to peptic duodenal stricture. Their ages were within the range of 17 to 70 years (mean, 41 years). Twenty eight patients (87.5%) were male and four (12.5%) were female. They had medical histories of duodenal ulcer between 4 and 40 years of age (mean, 12.8 years). All patients had a full diagnosis of 'pyloric stenosis' at the time of admission. Barium studies of the upper gastrointestinal tract revealed atonic and dilated stomachs in every patient. Similarly all patients had the typical symptomatology of gastric outlet obstruction.

Peptic duodenal stricture was due to a duodenal ulcer in most patients (81.2%). Pyloric channel ulcers constituted 18.7% of the series. Preoperative nasogastric decompression was used for an average of 2 days. Fluid and electrolyte replacement was necessary as a rule. Basal acid output and maximal acid output were determined in all patients. All patients were operated on either personally or under direct supervision of the author.

Parietal cell vagotomy was performed in all patients with the same method. Both anterior and posterior vagal trunks were identified and isolated on separate nontraumatic tapes as the initial step of the procedure. The esophagus was isolated on a penrose drain and retracted to the left. Lesser curve dissection was started immediately above the crow's foot. The posterior pancreatogastric attachments were cleared off and the angle of His was emptied from all neurovascular and connective tissue. The esophageal dissection was carried up to approximately 10 cm above the esophagogastric junction. A slight myotomy was performed at the lower esophagus to cut intramuscular vagal fibers, if present. The denervated lesser curvature was closed with interrupted 3/0 silk stitches in every case.

A small gastrotomy was performed at the denervated portion of the corpus, next to the gastric antrum, anteriorly, and toward the greater curvature. Hegar dilators were introduced through this opening, starting from the smallest-calibered dilator. The probe that could not pass the stricture without forceful manipulation was recorded

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as the caliber of the outlet. The initial outlet was between 6 to 12 Hegar (mean, 8.5 Hegar) in these 32 patients. Patients with less than a 10-Hegar outlet were considered to have a severe obstruction (75%, 24 patients), while those with an outlet between 10 to 12 Hegar had a moderate obstruction (25%, 8 patients). Dilatation was continued in a stepwise fashion, leaving the dilator within the stricture for a few seconds in each step. Dilatation was carried on until the stricture was felt to be relieved without doubt or until the largest dilator was introduced or until there was a duodenal rupture at the site of the stricture. Duodenal rupture complicated the dilatation process in five patients (15.6%) and was closed transversely with interrupted 3/0 silks sutures in every instance. A penrose drain was placed to the lesser curvature and maintained for 24 hours in patients without duodenal rupture and for 3 days for those with a rupture.

The nasogastric catheter was removed on the first postoperative day and patients generally were allowed to take oral fluids by the second day. Regular diet was resumed after the third postoperative day. Basal acid output and maximal acid output was determined when the patient was to be discharged from the hospital or 7 to 10 days after operation if the patient had been discharged. Gastric emptying was controlled with a barium meal when the patient resumed a regular diet and at 1 year follow-up. The patients were followed through a questionnaire and/or interview. Postoperative endoscopy was performed in all patients at the first year follow-up and then as indicated. Even slight symptoms were considered indications for a thorough search for recurrence.

Results

There were no hospital deaths. Significant morbidity was not encountered, except for one patient with prolonged gastrointestinal malfunction. This patient was a 59-year-old man with long-standing duodenal ulcer disease. The stricture in this patient was dilated from 7 to 19 Hegar, without rupture. He was discharged on the fifth day after operation but was readmitted 3 days later with abdominal distention, gastric retention, and faintness. There was no evidence of peritonitis. He was treated with nasogastric decompression, supportive measures, and intravenous fluids and he recovered in a few days. He has been Visick 1 since then.

Clinical Status

The patients have been followed for 1 to 10 years. A 5-year follow-up is available for 37.4% of the series, while 6- to 10-year follow-up is available for 62.4%. Late results were evaluated according to the Visick criteria. Visick 1 refers to excellent clinical status, Visick 2 to a good result, Visick 3 to a fair result, and Visick 4 to a poor result, including recurrences and reoperations related to a recurrence. At last follow-up 59.3% of the patients were classified as Visick 1 and 15.6% were Visick 2. Those with a good or excellent clinical outcome 1 to 10 years after operation for 74.9% of the patients in this series (Table 1).

Seven patients (21.8%) have had recurrence. Two of these patients (6.2%) were reoperated on in other hospitals. One patient was a 52-year-old woman with a moderate stricture dilated to 26 Hegar. She had been symptomatic starting from her third postoperative year and underwent a Billroth 2 gastrectomy 8 years after operation. The other patient was a 43-year-old man with severe stricture, dilated from 7 to 25 Hegar. At 1 year follow-up he was Visick 1. In his second postoperative year he had a recurrence and a subsequent perforation. He presented to a rural hospital, was treated with primary closure, but later died. This death apparently was related to recurrence.

Recurrence rates showed a stepwise increase in relation to the extent of the follow-up. The recurrence rate was 3.1% at 1 year, 9.3% at 5 years, and increased to 21.8% after 6 to 10 years follow-up. The recurrence rate for those patients initially diagnosed with a pyloric ulcer was 16.6% and for those patients with a duodenal ulcer the recurrence rate was 23%.

Apart from seven patients with a proved recurrence, there have been three other patients in whom a recurrence has been suspected. In two of these patients the reason for suspicion of a recurrence was gastrointestinal bleeding. However in both patients bleeding was attributed to gastric erosions with endoscopic examination. Both patients were under considerable stress related to family problems just before their episodes. Apart from this both patients have been classified as Visick 1 throughout their follow-up 7 and 8 years after operation. The third patient is the only one in whom a Visick 3 status has been assigned in this series. He had a severe stricture dilated from 8 to 24 Hegar, with a duodenal rupture and transverse closure. He had symptoms that interfered with his everyday life, but a recurrent ulcer could not be detected despite careful search. He has been lost to follow-up 1 year after operation and his current status is unknown.

TABLE 1. *Clinical Results After 1 to 10 Years Following Parietal Cell Vagotomy and Dilatation*

Visick Score	Percentage
1	59.3
2	15.6
1 + 2	74.9
3	3.1
4	21.8

Dilatation

The maximal dilatation performed in 32 patients with peptic duodenal stricture was between 17 and 26 Hegar (mean, 21.5 Hegar). Barium studies for gastric emptying revealed a free outlet in every patient, both immediately after surgery and during the first year of follow-up. Early restenosis did not take place. There has been only one instance of late restenosis (3.1%). This patient was a 70-year-old man with a severe stricture, dilated from 8 to 17 Hegar. He had been classified as Visick 1 for 5 years. After this time he experienced epigastric fullness and occasional vomiting; however repeated barium studies and endoscopy failed to reveal an ulcer. At his last follow-up, 9 years after operation, a recurrent ulcer and restenosis was detected. He responded very well to H_2-receptor blocker therapy and is completely free of symptoms.

Gastric Acidity

Gastric acidity was analyzed before operation and 7 to 10 days after operation in every patient. However nine patients refused to undergo acid studies at first year follow-up. Five of these were convinced for reanalysis during the second year follow-up. Hence acid secretory figures for preoperative, 7 to 10 days, and 1 or 2 years postoperative determinations are available in 28 of the 32 patients (87.5%).

The mean basal acid output (BAO) was 5.6 mEq/hour before parietal cell vagotomy (PCV) and dilatation. The mean early postoperative level of BAO, 7 to 10 days after surgery was 3.2 mEq/hour. Thus BAO was reduced by 42.86% immediately after PCV and dilatation. The mean BAO in the late postoperative period was 1.4 mEq/hour. Thus BAO was reduced by 75% 1 to 2 years after PCV and dilatation.

Maximal acid output (MAO) was determined after an intravenous injection of histamine dichloride, 0.04 mg/kg. The mean MAO was 30.1 mEq/hour before and 17.2 mEq/hour 7 to 10 days after PCV and dilatation. The immediate response of MAO to PCV thus was again 42.86%. There was a further reduction by 57.81% in the maximal acid output after 1 to 2 years after operation. The mean MAO, 1 to 2 years after PCV and dilatation was 12.7 mEq/hour.

Gastric acidity showed a different pattern in patients with a proved recurrence. Although the preoperative mean BAO was lower in patients with a subsequent recurrence (4.7 mEq/hour *versus* 5.6 mEq/hour for the entire group), the immediate response to PCV was not as marked. The mean BAO 7 to 10 days after operation decreased by 35% to a level of 3.1 mEq/hour. However late postoperative mean BAO was at the level of 1.5 mEq/hour 1 to 2 years after PCV and exhibited a 69% reduction compared to the preoperative level.

The mean preoperative MAO was higher in patients with a subsequent recurrence (34.9 mEq/hour *versus* 30.1 mEq/hour in the entire series). The mean MAO was 10.5 mEq/hour 7 to 10 days after operation, thus decreased by 70% in the immediate postoperative period. However this time a further decrease could not be seen 1 to 2 years after operation and the mean MAO increased to the level of 14.9 mEq/hour (a 58% decrease compared to the preoperative value or a 12% increase compared to the immediate postoperative level).

Discussion

More than 15 years have passed since the first report[3] of PCV and dilatation of the obstruction caused by chronic duodenal ulcer. The original intention was to reproduce the favorable early results of PCV in patients presenting with complications. Since then there have not been many published experiences with this procedure, and not surprisingly the results of PCV and dilatation have been conflicting.[4–6] The largest reported experience is based on 70 patients[7] and most of the reports are based on populations not exceeding 20 patients.[4–6,8–10] Furthermore the follow-up periods are variable, ranging from 0.7 to 10 years (Table 2). These factors may render results reported by individual authors less significant. An analysis of the collective data from 249 patients provided by the published literature[4–12] and this present series may lead to a more reliable decision on the results of PCV and dilatation.

The argument on the effectiveness of PCV and dilatation for the surgical treatment of peptic duodenal stricture ('pyloric stenosis') is based on the recurrence and restenosis rates. The recurrence rates reported vary between 6.6% after a minimum follow-up of 18 months[5] and 22.2% after 1 to 3 years follow-up.[4] The recurrence rate in this present series is 21.8%. On the other hand, there are reports with less[6,7,10] or no recurrence at all.[8,11]

TABLE 2. *Failure (Recurrence and Restenosis) Rates in 249 Patients (Including This Series) Collected from the Literature, Following PCV and Dilatation*

Reference	n	Visick 4 (%)	Restenosis (%)	Follow-up (Years)
McMahon, 1976[11]	23	—	—	1–5
Delaney, 1978[8]	11	—	—	1–3
Ferraz, 1981[4]	11	22.2	—	1–3
Rossi, 1981[9]	19	16		1.5 (minimum)
Dunn, 1981[5]	15	6.6		4–5
Blackett, 1981[7]	70	9	10	4 (mean)
Gorey, 1984[12]	44	16	18	5–7
Hooks, 1986[6]	14	11	5	0.7–5
Hom, 1989[10]	10	10	—	4
Menteş, 1989	32	21.8	3.1	1–10
Total	249	12	6.8	

Patients with duodenoplasty or drainage have been excluded.

The overall recurrence rate 1 to 10 years after PCV and dilatation in 249 patients is 12%. This is similar to the recurrence rates obtained after a mean follow-up of 10 years in 183 elective patients treated with PCV.[13] A recent review of the literature on PCV[14] also has presented data comparable with this rate. However almost all series on PCV and dilatation have follow-up periods shorter than 10 years and the late recurrence rate after PCV can be as high as 30% after 15 years.[15] The stepwise increase of recurrences from 3.1% after 1 year to 21.8% after 6 to 10 years in our series also suggests that the actual failure rate of PCV cannot be correctly determined before 10 years follow-up is completed. This trend justifies an expectation of a higher long-term recurrence rate than that after elective PCV in patients treated with PCV and dilatation.

One of the reasons why PCV and dilatation has not been used extensively seems to be related to the fear of failure to achieve a persistently patent and competent gastric outlet. At least two groups have suggested that poor results following PCV and dilatation could be improved if a drainage procedure had been added to PCV.[4,9] However there is both theoretical and clinical evidence that favors avoidance of a drainage procedure. Because motor nerves to the gastric antrum are preserved, it is assumed that PCV helps to maintain the propulsive activity of the stomach in an attempt to overcome the pre-existing obstruction and provides protection from restenosis.[3,11] Clinical evidence supports this point of view. Hooks et al.[6] compiled a series of 229 patients from the literature, with a restenosis rate of 4%. However their collective data consists of patients treated with PCV plus dilatation or duodenoplasty. We calculated a 6.8% restenosis rate in our collective series of 249 patients treated with PCV and dilatation. Most of the restenoses have been reported in two series.[7,12] Gorey et al.[12] have reported a restenosis rate of 18%, in which eight of the nine patients with recurrent stenosis had previously undergone patch closures for duodenal ulcer perforation. The ninth patient had an omental patch closure because of duodenal rupture during dilatation. Omental patches drawn to the duodenum are known to cause dense fibrosis[16] and these restenoses cannot be directly accepted as failures due to recurrent peptic strictures. Nevertheless restenosis does not seem to be a matter of major concern after PCV and dilatation and we share the view that a drainage procedure or duodenoplasty is unnecessary.[5]

Two possible methods for dilatation exist: finger dilatation and bougie dilatation. We have preferred bougie dilatation because the greatest diameter that can be achieved with finger dilatation would be 14 or 15 Hegar. The stricture in our patients were dilated to a mean of 21.5 Hegar (maximum, 26 Hegar) and we believe this has an influence on the low restenosis rate that we achieved. Despite the high rate of ulcer recurrence, only one patient (3.1%) experienced restenosis among our patients. The symptoms in this patient quickly resolved with H2-receptor blocker therapy 9 years after operation. Hence there is a high probability that even this was not a genuine restenosis.

One other important aspect of PCV and dilatation is that there is limited postoperative morbidity and almost no Visick 3 results during follow-up. Gastric emptying after PCV and dilatation is not different than that found after PCV alone for uncomplicated duodenal ulcer.[17] Although excellent results have been reported after PCV and drainage for obstructing duodenal ulcer,[2] this is not the case in every instance.[10,18] An additional drainage procedure does not have a significant influence on the recurrence rates[19] but may lead to immediate mechanical problems, as well as to late side effects, which are out of the question if the stricture is dilated instead. Dilatation has led to duodenal rupture in five patients (15.6%) in this series. However there is no other report of rupture comparable to our rate. This high rate may be due to the vigorous dilatation we used. A comparison of PCV and dilatation and truncal vagotomy and drainage has provided Visick 3 results of 4% and 22%, respectively.[11] On the other hand, when combined with dilatation, results after truncal vagotomy are comparable with those after PCV.[20] The only Visick 3 patient in this series probably should have ended with a recurrence if he could have been followed longer than 1 year.

In this present series, PCV resulted with a 43% reduction in BAO during the early postoperative period and with a 75% reduction 1 or 2 years after surgery. A similar decrease in MAO by 43% was achieved in the early postoperative period, while a 58% decrease was detected 1 or 2 years after PCV. These findings do not correlate with the assumption that PCV leads to a greater reduction in acid output during the initial phase and that there is a relative increase in gastric acidity after 1 year.[14] The acid secretion results in this series reveal that there is a stepwise reduction in both basal and maximal acid output during the first 2 years after PCV. This trend was impaired in relation to maximal acid output in response to a dose of histamine dichloride in patients with a subsequent recurrence. Data has been presented on the prediction of a recurrence,[14] however uniformly valid predictive acid secretory criteria are not present. Because almost all recurrences in this series occurred after the third postoperative year, our data suggest that an increase in MAO within 2 years after an initial decline may raise concern of a recurrence for the patient in question.

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Intrarectal Ultrasonography in Rectal Cancer Staging and in the Evaluation of Pelvic Disease

Clinical Uses of Intrarectal Ultrasound

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Accurate preoperative staging of a rectal cancer patient may impact heavily on subsequent management. This study attempts to evaluate the accuracy of intrarectal ultrasonography (IRUS) in staging rectal cancers compared to clinical and pathologic examination. In addition the accuracy of IRUS was assessed in a group of patients with uncertain pelvic-perirectal disease after a negative physical examination. In a prospective manner, 52 cancer patients were staged with digital exam and IRUS. Accuracy rates were 48% and 83%, respectively, compared to pathologic evaluation in assessing wall penetration, and IRUS identified positive lymph nodes in 12 of 17 cases. In patients with pelvic disease, IRUS corresponded with pathologic diagnosis in 15 of 17 cases and revealed new information in 6 patients. Intrarectal ultrasonography appears to be the most accurate imaging technique for staging rectal cancers and demonstrates promise in the evaluation of perirectal-pelvic disease.

ACCURATE PREOPERATIVE STAGING of rectal cancer has become increasingly important due to a renewed interest in local excision of small cancers[1] and reported use of preoperative radiotherapy to lower local recurrence rates.[2] Digital examination has an accuracy rate of only 60% to 70% in small rectal lesions[3,4] and intrarectal ultrasound (IRUS), initially used for evaluation of prostatic diseases,[5] has been adapted for staging of rectal cancer during the last decade.[6–14]

The present study includes a prospective section that compares the accuracy of digital examination and IRUS in staging rectal cancer. In addition a second group of patients with nonspecific pelvic or perirectal pain were evaluated using IRUS. Physical examination, endoscopy, conventional pelvic ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) are the principal modalities available to assess pelvic structures. The use of IRUS has been reported only briefly in diagnosing extrarectal disease,[15] but because the focal length (2 to 5 cm) of instruments used today allows visualization of perirectal structures, we evaluated the usefulness of IRUS in a consecutive series of patients.

Materials and Methods

All patients were examined on an outpatient basis without anesthesia. The equipment used was a Bruel and Kjaer 1846 ultrasound scanner with a rotating hand-held endoprobe equipped with a 7.0-MHz transducer having a focal length of 2 to 5 cm. The endoprobe was either introduced blindly into the rectum or placed at the level of a lesion through a specially constructed rectoscope with the patient lying in the left lateral decubitus position. In the several cases of previous proctectomy in women, the probe was passed transvaginally. After placement in the lumen, a latex balloon that covers the transducer was inflated with degassed water for good ultrasonic contact.

Staging of Rectal Cancer

In a prospective fashion and using a standardized protocol, patients with rectal cancer were evaluated with digital examination (performed by the responsible surgeon) and with ultrasonography (performed by an independent investigator [JWM]). Fifty-two patients (35 men, 17 women; median age 73 years; range, 28 to 74 years) who subsequently underwent surgery are included in this study.

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In seven patients a local excision was performed and these patients are not included in the analysis of lymph node involvement. Due to stenotic lesions, the IRUS probe could not be passed beyond the tumor in two cases. In 10 patients the tumors were located above the reach of the examining digit. The Astler-Coller modification of the Dukes' staging system was used[16] in clinical, ultrasound, and pathologic staging. Test results were compared by an independent investigator.

Evaluation of Uncertain Pelvic Disease

Results of IRUS in the study group with uncertain pelvic perirectal disease were compared to pathologic evaluation of tissue removed and, in eight cases, to pelvic CT scans. Twenty-four consecutive patients (8 men, 16 women; median age 55 years; range, 21 to 74 years) were examined by routine physical examination, digital-rectal, and, when appropriate, vaginal examination. Presenting symptoms were (1) pelvic or perianal pain in 14 cases, (2) perianal or pelvic mass in 5 cases, and (3) miscellaneous other diagnosis in 5 patients. Again all IRUS examinations were performed by one investigator (JWM). Statistical significance in the rectal cancer study was assessed using the x^2 and Fisher's exact test.

Results

Overall the IRUS examinations were performed without complications, in less than 25 minutes, and were minimally uncomfortable.

Staging of Rectal Cancer

In the cancer study group, prediction of wall penetration was significantly better with IRUS compared to clinical examination (accurate in 43 of 52 cases (83%) *versus* 20 of 42 cases (48%); $p < 0.05$). Digital examination correctly delineated involvement of regional lymph nodes in 1 of 15 cases and IRUS was correct in 12 of 17 cases ($p < 0.05$). A comparison of sonographic assessment and pathologic staging (combining wall penetration and lymph node status) is outlined in Table 1, which shows understaging with IRUS in 10 patients, overstaging in 6 patients, and overall correct staging in 36 patients.

TABLE 1. *Comparison of Sonographic Assessment and Pathologic Staging (Astler-Coller) in 52 Patients with Rectal Cancer*

		Ultrasound				
Histology	n	A	B1	B2	C1	C2
A	9	5	2	2		
B1	3		3			
B2	21		3	16	1	1
C1	1			1	0	
C2	18		1	5		12

n, number of patients.

Evaluation of Uncertain Pelvic Disease

In the patients with uncertain perirectal pelvic disease, IRUS diagnosis correlated with pathologic diagnosis in seven of eight patients with pelvic pain. The other six patients in this group had normal IRUS studies, and thus no tissue diagnosis was made. One patient had a false-positive exam for a pelvic mass (? abscess), which, at surgery, was thought to be a loop of intestine.

In the group with pelvic or perineal mass, IRUS corresponded to pathologic diagnosis in four of five cases, and in all five patients with miscellaneous conditions IRUS correctly predicted pathologic diagnosis.

Overall IRUS diagnosis (Table 2) correctly corresponded with pathologic diagnosis in 15 of the 17 cases in which a tissue diagnosis was obtained. Completely new information not suggested by routine physical examination and endoscopy was obtained using IRUS in 6 of the 24 patients studied.

TABLE 2. *Intrarectal Ultrasound Findings in Patients with Uncertain Perirectal Disease*

Finding	n
Abscess	5
Pelvic tumor	4
Mass	4
Endometrioma	1
Fat necrosis	1
Lymph node metastasis	1
Retained cervix	1
No diagnosis	7

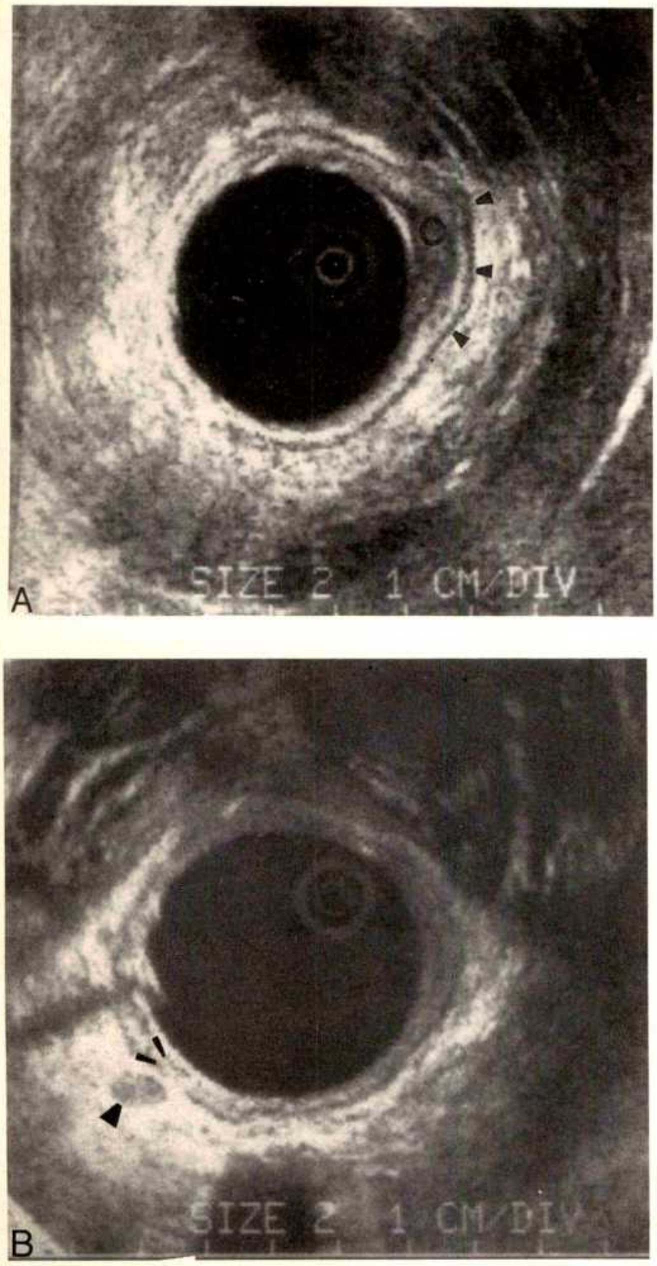
n, number of patients.

Only one of the seven patients with a normal study had persistent problems—in this one patient, a pelvic abscess was found at 6 months follow-up. It is impossible to know if this abscess was present earlier.

Of the eight patients undergoing CT scan of the pelvis, three patients with negative CT scans had abnormalities detected only by IRUS examination; all were later confirmed histologically.

Discussion

Various methods have been used to evaluate wall penetration and status of mesorectal lymph nodes in rectal cancer. Digital examination is most commonly used, is convenient, and forms an important part of the initial evaluation of a rectal cancer patient. Limitations of digital rectal examination include its subjectivity, the fact that accuracy is related to clinical experience, and the fact that only the distal 8 to 10 cm of rectum may be staged with this technique.[4] The accuracy of digital rectal exam for lymph node status is no more than 50% and its accuracy in predicting wall penetration ranged from 33% to 80% in two clinical series.[3,4]



FIGS. 1A and B. (A) Endoluminal ultrasound study demonstrating a rectal cancer (C) invading into but not through the muscularis propria, represented by the thick dark line (arrowheads). The large black circle represents the water-filled balloon inside the rectum, with the two white concentric rings representing the ultrasound transducer. (B) Endoluminal ultrasound study demonstrating a histologically proved lymph node, involved with metastatic adenocarcinoma, located just outside the right posterior quadrant of the rectum (large arrowhead). The two ultrasonographic dark layers of the rectal wall are seen adjacent to the node (small arrowheads), the outer one corresponding to the muscularis propria, the inner one to the mucosa-submucosa.

TABLE 3. *Cumulative Results of Lymph Node Involvement in 404 Patients Comparing Intrarectal Ultrasound with Pathologic Findings (from references 9, 11 to 13, 21, plus the present series)*

	Ultrasound	
Histology	N−	N+
N−	193	47
N+	32	132

Sensitivity, 81%; specificity, 80%; positive predictive value, 74%; negative predictive value, 86%.

N−, no lymph nodes involved with metastatic cancer.

N+, lymph node(s) involved with metastatic cancer.

In early studies rectal cancer staging using CT scan[17] or MRI[18] showed high accuracy rates for locally advanced tumors (80% to 90%) but small to moderately sized tumors were sometimes difficult to locate using these new diagnostic modalities. Overall accuracy rates in recent series have ranged from 48% to 79%.[13,19,20] In addition layers of the rectal wall, critical components of all standard rectal cancer staging systems, are seen using IRUS but are not visualized with CT or MRI.

In this prospective study, IRUS has been shown to be significantly more accurate than digital examination in estimating wall penetration and lymph node involvement when staging by both techniques were compared to pathologic staging by an independent investigator unaware of the clinical status of the patient (Fig. 1). This series's 83% accuracy rate for wall penetration evaluation is similar to earlier reports,[7,10,13] although comparisons are difficult due to the use of different pathologic staging systems. Thus it is reasonable to include IRUS in the preoperative evaluation of a patient with rectal cancer in which local excision is an alternative.

As late as 1985, it was reported that IRUS was unable to determine lymph node involvement,[7] but subsequent studies[9,11-13,21] proved this statement to be false. Table 3 summarizes data from six series on this subject, showing that IRUS has high sensitivity and specificity rates for the evaluation of lymph nodes adjacent to a rectal cancer. However it is still debatable if the results of a preoperative IRUS examination in patients with large rectal tumors can predict whether preoperative radiation would be beneficial.

The use of intrarectal ultrasonography to assess extrarectal pelvic structures has been mentioned briefly in the literature[15] (Fig. 2). The first described use of this technology, reported in 1956, was to visualize a recurrent rectal tumor outside the bowel lumen.[22] Better methods of evaluation of the patient with pelvic or perineal symptomatology clearly are needed—symptoms are often nebulous, the examination may be embarrassing and painful, and conventional imaging modalities may suffer a fall-off in

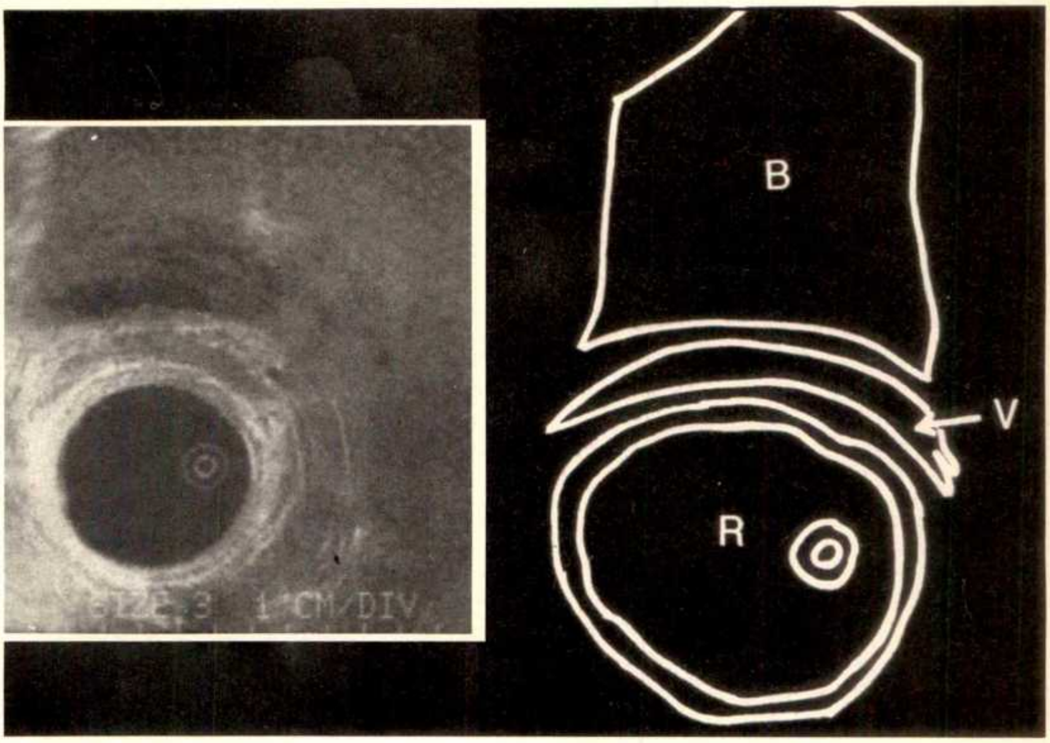


FIG. 2. Normal pelvic endoluminal ultrasound image and diagrammatic interpretation (on right) using a 7.0-MHz transducer demonstrating clear resolution of the rectum (R), vagina (V), and part of the bladder (B).

accuracy rates in this region compared to other areas of the body.[23,24]

Intrarectal ultrasonography provided new information in 25% of 24 patients with uncertain pelvic disease when routine history and physical examination did not. In addition in three of the eight patients in whom CT scan of the pelvic region was negative, endoluminal ultrasonography revealed new, clinically relevant information. Because this test may be performed rapidly with minimal patient discomfort, IRUS should be considered early in the management of patients with uncertain pelvic problems.

This series shows that IRUS is a safe, expeditious, and accurate imaging modality for staging rectal cancer and for diagnosing patients with uncertain pelvic disease. It possesses the highest accuracy rate for assessing depth of wall penetration in rectal cancers of any current imaging modality, and furthermore appears to be the only imaging technique capable of assessing adjacent lymph nodes. Taking into consideration the recently shown benefits of endoluminal ultrasonography in the follow-up of patients after rectal cancer surgery[25] and in the evaluation of perianal sepsis–anal fistula,[26] it seems that the role of ultrasonography is expanding in the diagnostic armamentarium of anorectal diseases. Future efforts focusing on common protocols and carefully defined data points are needed to precisely define the role of IRUS in pelvic disease management.

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Localization and Peptide Content of Endocrine Pancreatic Tumors

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Endocrine pancreatic tumors contain and frequently secret neurohormonal peptides. This phenomenon can be used as a diagnostic and classifying tool. This study analyzes 31 patients operated on because of an endocrine pancreatic tumor, including the diagnostic procedures and the localization methods. In 15 insulinoma cases only 6 patients had a positive arteriography, while all 11 selective pancreatic vein samplings were positive. The immunoreactivity showed that, besides insulin, most tumors also contained other peptides. Of four gastrinoma cases the arteriography was positive in three, but the selective vein sampling localized the tumor in all. The tumors's content of peptides showed mixed patterns. In the four glucagonomas, the arteriography was positive in all and the venous sampling performed in three of the cases also was positive. In five pancreatic polypeptide-containing tumors (PP-omas) the arteriography was positive in four and sampling performed in two was positive in both. In the PP-omas the peptide pattern showed that these tumors frequently contain several peptides. We used selective pancreatic vein sampling in 21 cases with positive result in all. In the cases in which arteriography was negative, the sampling results helped the surgeon to find the tumor. The peptide pattern in the tumors varied greatly and most tumors were multihormonal.

ENDOCRINE TUMORS OF the pancreas are rare, but when they do occur the patients may suffer considerably before diagnosis is reached and the tumor is removed. In one important aspect endocrine tumors are different from other tumors arising in the pancreas. They produce neurohormonal peptides in varying degrees, which, in many cases, can be analyzed by radioimmunoassay.[1] This fact makes is possible to use neurohormonal peptides as tumor markers aiding in the diagnosis by measuring elevated fasting levels in the blood.[2,3] The development of stimulation and suppression tests has increased the sensibility and diagnostic reliability even more.[4,5]

The true incidence of endocrine pancreatic tumors is difficult to estimate because many of these tumors are silent. However the distribution of various types of islet cell tumors is documented in several series.[6,7] The most common tumor is insulinoma (50% to 60%), followed by 'nonfunctioning' tumors (15% to 25%), gastrinoma (18% to 20%), and various types (7%).

Once the diagnosis is established, the question arises of where the tumor is localized within the pancreas and whether it is solitary or multiple. The noninvasive preoperative localization methods of choice are sonography and computed tomographic (CT) scanning. Sonography has been shown to be positive in 63% to 90% of cases, and CT scan is positive in 45% to 90% of cases, as compiled from several studies.[8-11] Arteriography is an invasive examination with an accuracy rate of 40% to 90% and a false-positive rate of about 5%.[8,9,11] The abnormal release of neurohormonal peptides from the tumors has enabled their localization by sampling blood from various branches of the portal or intestinal veins. This method, however, is highly invasive and the outcome depends on the skill of the investigator. The reported results are thus poor (60% positive) when the sampling is done in the main portal branches; they are much better, however (80% to 90% positive), when a superselective sampling is made.[8] Since the early 1970s we have used the superselective sampling technique for the localization of different gastrointestinal endocrine tumors and their metastasized areas.[12]

Some gastroenteropancreatic endocrine tumors behave more aggressively than others of the same size and extent of metastasis. Therefore to obtain prognostic information, analyses of growth pattern, peptide content, and patterns

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of DNA distribution in carcinoid tumors have been made, but without consistent results.[13] Hence the treatment strategy of gastroenteropancreatic endocrine tumors is still surgical intervention. To achieve radicality a preoperative mapping of the tumor extent is essential.

A number of investigations have shown that endocrine pancreatic tumors frequently are multihormonal, *i.e.*, contain several neurohormonal peptides.[14–16] Such tumors are composed of multiple endocrine cell types, some of which are not seen in the normal adult pancreas. For several peptides there are reports also on elevated plasma levels in patients with pancreatic endocrine tumors.[17] It is also noteworthy that the metastasized areas may contain a different set of peptides than the primary tumor.

In this series we report our experience with pancreatic vein catheterization with blood sampling to localize 31 pancreatic endocrine tumors treated at our department.

Because it cannot be excluded that the peptide content

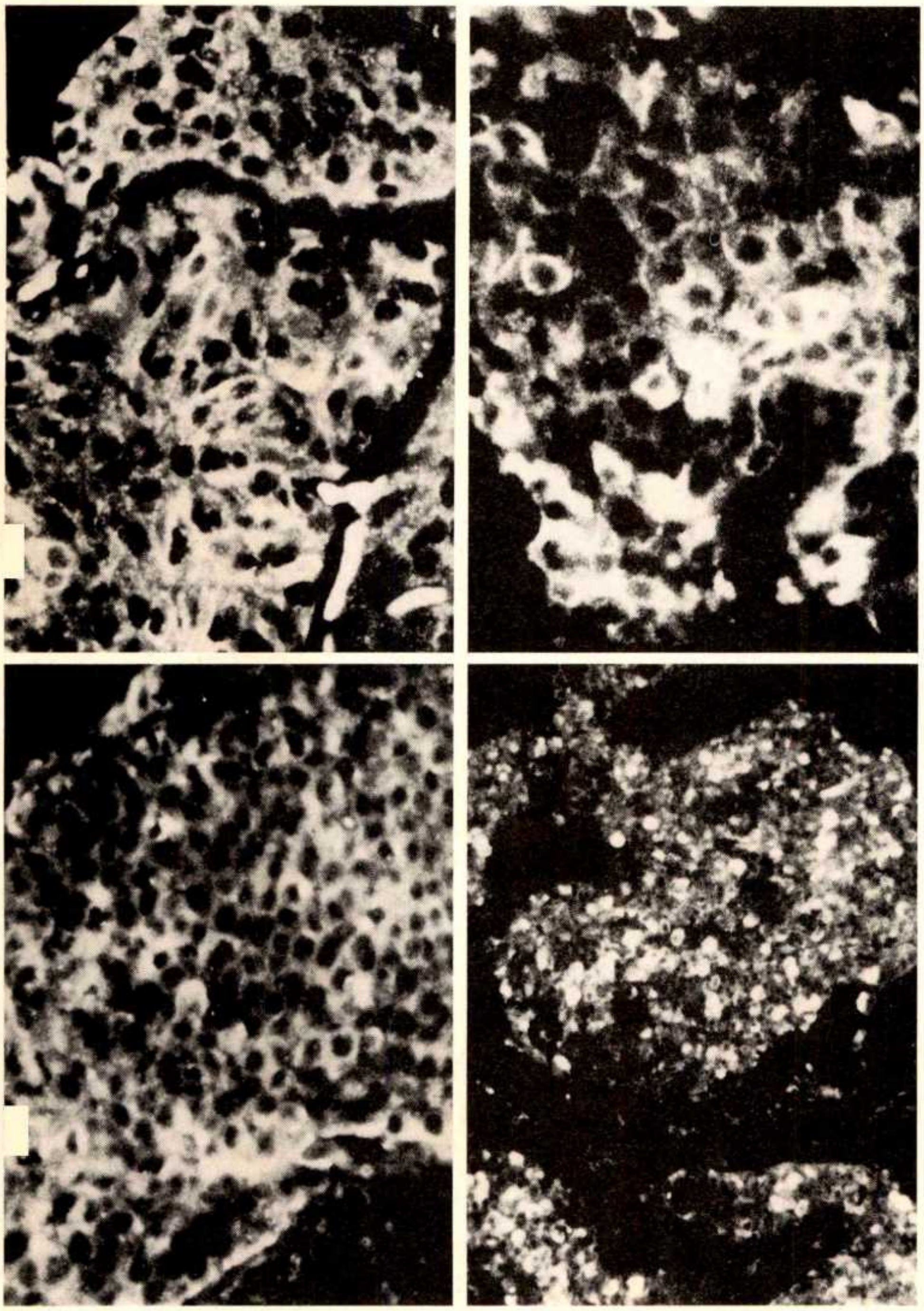

FIG. 1. Sections from two insulinomas immunostained for chromogranin A (upper left [a] and upper right [b]; 350×) and for insulin (lower left [c] and lower right [d]; 250× and 100×). Most of the cells display chromogranin- and insulinfluorescence of varying intensity. In [d] intensely insulin-immunoreactive cells occur among the more weakly stained ones.

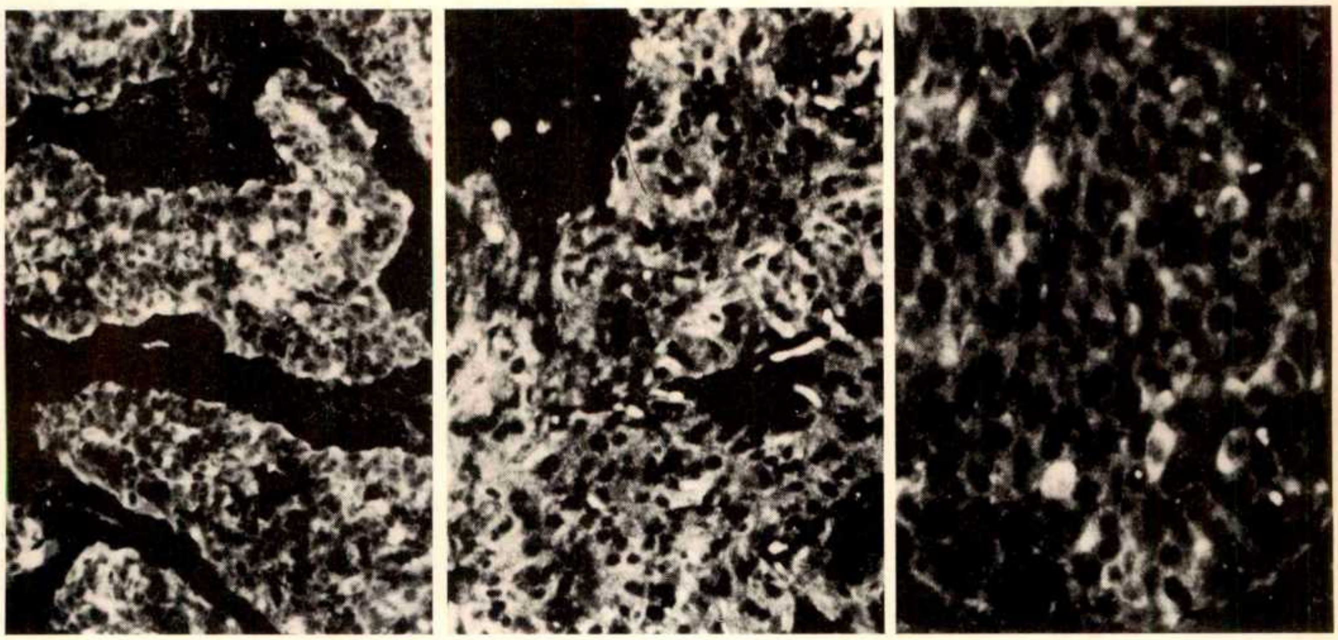

FIG. 2. Two insulinomas immunostained for insulin (left [a] and middle [b]; 175×). The immunoreactive cells display slightly different growth patterns. Some insulinomas also contained single scattered gastrin-immunoreactive cells (right [c]; 300×).

and pattern in the tumor may be related to the aggressiveness of the disease, we re-examined all tumor specimens available with respect to their peptide content and distribution as demonstrated by immunocytochemistry.

Materials and Methods

The records of 31 patients operated on because of a suspected pancreatic endocrine tumor were reviewed. The analysis encompassed clinical picture, patient age, time from start of symptoms to diagnosis, diagnostic procedures, localization methods, type of operation, tumor size and number, extent of metastasis, and survival.

The pancreatic vein sampling was performed using techniques previously published from our hospital.[12]

Tumor tissue specimens available were re-examined using immunocytochemistry with respect to the content of neurohormonal peptides and serotonin. However none of the three islet cell hyperplasias was available for reexamination.

Most pancreatic specimens, or metastasized areas, were obtained at surgery and fixed on either 4% phosphate buffer (pH 7.3; 1.5 mol/L [molar]) formaldehyde or on Bouin's solution (4% formaldehyde, 1% picric acid, 0.5% acetic acid) for 18 hours. The specimens were dehydrated through a graded series of alcohol, embedded in paraffin, and sectioned at ± 5-μm thickness.

The hydrated solutions were processed for fluorescence or peroxidase indirect immunocytochemistry[18] using primary antisera to insulin, glucagon, somatostatin, pancreatic polypeptide (PP), gastrin, Pro-ACTH, calcitonin (CT), calcitonin gene related peptide (CGRP), PYY, Galanin, or serotonin.

Results

The tumors comprise 15 insulinomas, of which 3 were islet cell hyperplasias, 5 gastrinomas, 5 pancreatic polypeptide-containing tumors (PP-omas), 4 glucagonomas, and 2 unclassified tumors. The tumor classification is based on the clinical symptoms, except for PP-omas, in which the main peptide released from and/or contained in the tumor formed the basis. From one of the two unclassified tumors, specimens were not available for re-examination and the other showed no immunocytochemical reaction.

Insulinomas

Of the 15 patients, there were 11 women and 4 men, with a mean age of 57 years (median, 60 years; range, 32 to 83 years). The main symptoms were disturbances in consciousness in 14 patients, fatigue in 7 patients, and weight gain in 2 patients. Most patients were diagnosed within 1 year. In two patients, however, the time from onset of symptoms to diagnosis was more than 3 years. Fasting test with monitoring of insulin-glucose ratio was performed in 12 patients, and all were positive within 24 hours (Table 1). Arteriography was undertaken in 15 patients but was positive in only six patients (Table 1). A selective pancreatic vein sampling was performed in 11 patients, which resulted in correct localization of the tu-

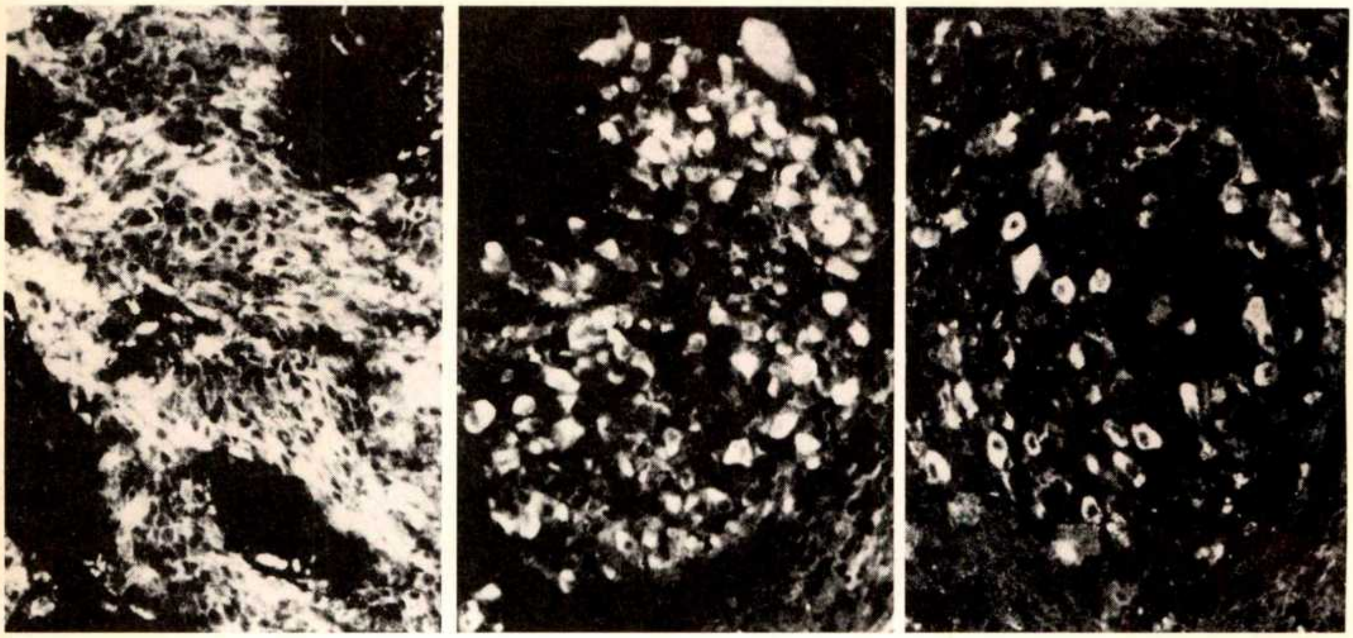

FIG. 3. Two glucagon-containing tumors (left [a]; 175×, and middle [b]; 200×). Note the different growth pattern and the different arrangement of glucagon cells in the two tumors. At the right, [c]; 200×, a section from the tumor shown in [b] was immunostained for PP. PP-immunofluorescent cells occur scattered in the tumor.

mor in all cases (Table 1). The mean ratio of peptide level between a tumor-draining vein and a large vein was 18.8 to 1.

Surgery consisted of enucleation in 1 case, tail resection in 10 cases, and Whipple's operation in 1 case. The tumor was solitary in all the cases and the size of each tumor is listed in Table 1. All operations were considered radical, and no patient has died from an insulinoma.

The results from immunocytochemical analysis are schematically shown in Table 2A. All tumors were immunoreactive for insulin, 2 tumors had 1 more peptide, 2 tumors had 2 more peptides, 2 tumors had 3 more peptides, and 1 tumor had 5 more peptides (Figs. 1 and 2). Only one tumor contained immunocytochemically demonstrable serotonin (Table 2 A).

Gastrinomas

Patients with grastrinomas included two women and three men. Their mean age was 44 years (median, 42 years;

TABLE 1. *Insulinomas. Some Clinical Characteristics and the Result of Localization Procedures*

Patient								Pancreatic Vein Sampling		
No.	Sex	Age (years)	Tumor Size (mm)	Arteriography	CT Scan	Sonography	Fasting	Result	Tumor Vein	Other Vein
1	F	67	10	+	ND	ND	+	+	6200 μU/mL	179
2	F	74	40	−	+	ND	+	ND	ND	ND
3	F	82	10	−	ND	+	+	+	308	131
4	F	68	20	−	−	−	+	+	7317	145
5	F	52	20	−	−	−	+	+	>400	170
6	F	41	?	+	−	ND	+	+	>400	21
7	F	40	8	−	ND	−	+	+	>400	27
8	F	37	Hyperplasia	−	ND	−	+	+	245	24
9	F	32	Hyperplasia	+	ND	ND	ND	+	1130	45
10	F	61	15	+	ND	ND	ND	+	704	95
11	M	60	30	−	ND	ND	+	ND	ND	ND
12	M	62	Hyperplasia	+	+	ND	+	+	170	8
13	M	72	30	+	ND	ND	ND	ND	ND	ND
14	M	55	12	−	ND	−	+	+		
15	F	62	?	−	ND	ND	+	ND	ND	ND

F, female; M, male; ND, not done; + positive localization; − negative localization.

TABLE 2. *The Immunocytochemical Staining Pattern*

	Patient	Insulin	Glucagon	Somatostatin	PP	Gastrin	Pro-ACTH	CT	PYY	CGRP	Galanin	Serotonin
A	2	+	−	−	−	−	+	−	−	−	−	−
	3	+	−	−	−	−	−	−	−	+	−	−
	4	+	−	−	−	−	−	−	−	−	−	−
	5	+	−	+	+	−	+	−	−	−	−	+
	6	+	−	−	−	−	−	−	−	ND	ND	−
	7	+	+	−	−	−	−	+	ND	ND	ND	ND
	10	+	+	+	+	−	+	−	−	−	+	−
	11	+	−	+	+	−	−	−	−	−	+	−
	13	+	−	+	−	−	−	−	−	+	−	−
	14	+	−	−	−	−	−	−	−	−	−	−
B	1	−	−	−	+	+	−	−	−	+	−	−
	2	+	+	−	+	−	+	−	−	+	−	−
	3	+	−	+	−	+	−	−	−	−	−	−
	4	−	−	−	−	+	−	−	ND	ND	ND	ND
	5	−	−	−	+	+	−	−	ND	ND	ND	ND
C	3	−	+	+	−	−	ND	ND	ND	ND	ND	+
	4	−	+	−	−	−	−	−	ND	ND	ND	ND
D	1	+	+	−	+	−	−	−	−	+	−	−
	2	−	−	−	+	−	−	−	ND	ND	ND	ND
	4	+	+	−	+	+	+	−	−	−	+	−
	5	−	−	+	+	−	−	+	+	+	−	−

A, insulinomas; B, gastrinomas; C, glucagonomas; D, PP-omas; + positive immunoreactivity; − negative immunoreactivity; ND, not done.

range, 34 to 54 years), and the main symptom was recurrent ulceration. Two patients had perforating ulcers, of which one was situated in the proximal jejunum and the other in the proximal duodenum. Two patients had symptoms for more than 15 years, 1 patient for 3 years, and 2 patients for less than 1 year before diagnosis was established. Basal gastrin levels were increased in all patients (Table 3). A secretin provocation test was performed in three patients: all of them responding with excessive release of gastrin. Arteriography was performed in four patients, with a positive localization in three. Selective pancreatic vein sampling in all four patients localized the tumor in all (Table 3). The mean ratio of peptide level between a tumor-draining vein and a largeig vein was 4.4 to 1.

In three patients a total gastrectomy was performed before the pancreatic surgery. A tail resection was performed in three patients; in one patient the tumor was enucleated, and in one patient a biopsy was performed. One patient had a solitary tumor, three had multiple, and one had a large mass in the pancreas. The diameter of the tumors ranged between 15 and 25 mm. One patient had no metastasis, two had lymph node metastasis, and two had liver metastasis. None of the patients died from the gastrinoma, and the two with liver metastasis are free from symptoms. Three of the patients were categorized as multiple endocrine neoplasia type I (MEN I).

The immunocotychemical results are shown in Table 2B. One tumor contained no immunocytochemically demonstrable gastrin but five other peptides, and in another tumor only gastrin could be demonstrated. One tumor contained one more peptide and two tumors had two more peptides. None of the tumors contained serotonin-immunoreactive cells.

Glucagonomas

There were two women and two men aged 45, 63, 62, 69 years, respectively. The symptoms in all patients were

TABLE 3. *Gastrinomas. Some Clinical Characteristics and the Result of Localization Procedures*

Patient			Tumor Size (mm)	Arteriography	CT Scan	Sonography	Secretin Test	Pancreatic Vein Sampling			Gastrin Basal Level
No.	Sex	Age (years)						Result	Tumor Vein	Other Vein	
1	M	52	?	+	+	ND	ND	+			1100 pg/ml
2	F	38	15	ND	ND	ND	+	ND	ND	ND	587
3	M	42	15	+	+	ND	ND	+	>5000	500	
4	M	54	25	+	ND	ND	+	+	776	424	470
5	F	34	?	−	ND	ND	+	+	2380	1720	8200

F, female; M, male; ND, not done; + positive localization, − negative localization.

TABLE 4. *Glucanomas. Some Clinical Characteristics and the Result of Localization Procedures*

Patient			Tumor				Pancreatic Vein Sampling			
No.	Sex	Age (years)	Size (mm)	Arteriography	CT Scan	Sonography	Result	Tumor Vein	Other Vein	Glucagon Basal Level
1	F	63	?	+	ND	ND	ND	ND	ND	Normal
2	M	62	20	+	ND	ND	+	24,000 pg/mL	1540	1500
3	F	45	50	+	ND	ND	+			87
4	M	69	40	+	ND	−	+	10,000	550	1850

F, female; M, male; ND, not done; + positive localization; − negative localization.

diabetes and skin rash. Basal levels of circulating glucagon were increased in three patients (Table 4). The time elapsing from the start of symptoms to diagnosis was 2, 4, 6, and 7 years. Arteriography was performed in all patients, and selective pancreatic vein sampling in three patients, and all were positive (Table 4). The mean ratio of peptide level between a tumor-draining vein and a large vein was 16.9 to 1. One patient had a portal occlusion that prevented portal vein catheterization. Surgery consisted of biopsy in 1, enukleation in 1, and tail resection in 2 patients. All tumors were solitary and measured 20 to 40 mm in diameter. Before operation none of the patients had signs of metastasis. At surgery one patient had a large mass in the pancreas, while the others had no signs of metastasis. However after operation liver metastasis developed in one patient and another patient has increased blood glucagon levels.

Two glucagonoma tumors were available for re-examination (Fig. 3). One contained only glucagon and the other also contained somatostatin and serotonin (Table 2C).

PP-omas

Of the patients with PP-omas, there were four women and one man who were aged 55, 55, 59, 70, and 37 years, respectively. Two patients had no symptoms while three had diffuse abdominal pains. The tumors were discovered during investigation for pains or incidentally at surgery for other reasons. Basal plasma levels of PP were increased in 3 patients, normal in 1, and were not measured in 1 patient. Arteriography was performed in all patients and was positive in four. Selective pancreatic vein sampling was done in two of the patients and was positive in both (Table 5). The mean ratio of peptide level between a tumor-draining vein and a large vein was 4.3 to 1. Arteriography failed to produce positive results in the patients lacking increased levels of PP in blood. Two patients were operated on with the Whipple procedure, while from the others only biopsies were taken. The tumors were solitary, ranging in diameter size from 25 to 50 mm. Four patients had liver metastasis and one had lymph node metastasis. One patient died 4 years after diagnosis and three died within 1 year. The only survivor (at 5 years) was the patient with lymph node metastasis.

Four PP tumors were available for re-examination and the immunocytochemical results are shown in Table 2D. All tumors contained PP, 1 had another 3 peptides, 1 had 4, and 1 had 5 more peptides. Only one tumor contained only PP. No serotonin was found in these tumors.

Discussion

Endocrine pancreatic tumors are rare, but when they do occur they may cause specific symptoms leading the physician to make an accurate diagnosis.[19] With modern techniques the relevant neurohormonal peptides may be identified under basal conditions and after stimulation or inhibition.[19] The combination of symptoms and peptide analysis has improved the accuracy of diagnosis.

The treatment of a patient with pancreatic endocrine

TABLE 5. *PP-omas. Some Clinical Characteristics and the Result of Localization Procedures*

Patient			Tumor				Pancreatic Vein Sampling			
No.	Sex	Age (years)	Size (mm)	Arteriography	CT Scan	Sonography	Result	Tumor Vein	Other Vein	PP Basal Level
1	F	70	50	−	−	+	+	51 pmol/L	8	Normal
2	F	55	30	+	+	+	+	299 μg/mL	131	212
3	F	55	30	+	ND	ND	ND	ND	ND	ND
4	M	37	25	+	+	ND	ND	ND	ND	150000 pmol/L
5	F	59	?	+	+	+	ND	ND	ND	30000 pmol/L

F, female; M, male; ND, not done, + positive localization; − negative localization.

tumor has been, and still is, primarily surgery with the aim of radical excision. When this is not possible, an extensive reduction of tumor mass is desirable. Generally it is agreed that medical treatment with cytotoxic agents or interferon should be used when surgery is not possible or not radical.[20-22] To make surgery optimal, preoperative localization of the tumors and possible metastasized areas is needed. We used superselective pancreatic vein catheterization with blood sampling in 21 cases. In all of these cases the result was positive and helped the surgeon to find the tumor. It is noteworthy that some of the insulinomas measured 12 mm or less in size, but still the sampling provided data of peptide secretion. This is even more interesting because the corresponding arteriography in these cases was negative. The advantage with the sampling technique is that it may detect small tumors where other methods fail. Only in one case was the sampling hard to interpret despite a tumor size of 5 cm: a PP-oma patient in whom the tumor contained immunoreactive PP, insulin, and glucagon, but none of the peptides displayed elevated levels in the plasma samples. This may be explained by the fact that none of these peptides were released. One possibility to overcome this may be the use of stimulation test during the sampling,[5] but so far we have not used that. Therefore an uncertain or negative result of sampling may be caused by lack of neurohormonal peptide secretion or, alternatively, by the secretion of a defect peptide or a peptide fragment not picked up by the radioimmunoassay.

In the 15 insulinoma cases it is interesting to note that nine arteriographies (60%) were negative while all samplings were positive. A small tumor size is not likely to be the cause of this because some of them were large and arteriography in other small tumors was positive. One possible explanation is that the vascularity of the insulinomas may be different when compared to other endocrine pancreatic tumors, thus explaining the difference in accuracy of the arteriography.

Previously we calculated the arteriovenous difference in the sampling technique for localization of gastroenteropancreatic tumors.[12] The interpretation of peptide values in the pancreatic vein sampling was without problems in all patients but one in this study, whereas the peptide levels expressed as the ratio between a tumor-draining vein and a larger pancreatic or portal vein were high in all the cases. The problem case is illustrative with absolute values almost normal, but the ratio being 6.5 to 1. Therefore we stopped using the technique of measuring the arteriovenous difference. The absolute value and/or the ratio between a tumor-draining vein and a large vein seems to give the same information and the patient is relieved from one catheter. However it must be pointed out that it is not necessary to perform selective pancreatic vein catheterization and sampling in all cases of endocrine pancreatic tumors. For example insulinoma tumors usually are solitary. Hence a positive result of clinical, laboratory, and less invasive localization procedures may be sufficient for a preoperative work-up.

The multipeptide content of the tumors showed a variety of patterns. No conclusions could be drawn regarding the tendency for the tumors to metastasize or to follow a more malignant course. The only exceptions were the PP-omas in which two patients died a few months after the diagnosis was established with, respectively, four of five additional peptides in the tumor. Possibly the presence of many peptides indicates a lesser degree of differentiation and more aggressive growth of the tumor. These two patients had extensive liver metastasis as well. Further studies are needed to substantiate this.

The criteria used for the classification of endocrine tumors have changed considerably during the last 20 years. It may be based on clinical symptoms, conventional histology, ultrastructural features, immunocytochemical findings, or circulating hormone levels. Previously it was shown that pancreatic endocrine tumors may contain a variety of peptides distributed in different cell populations.[23] Furthermore there can be differences in the tumor cell composition between metastasized areas and the primary tumor.[24] This study also confirms previous results indicating that most of these tumors are multihormonal. Even if we have not been able to show a consistent pattern, determining the tumor peptide content (or release) may be a possible method to subclassify pancreatic endocrine tumors. Therefore it particularly important that these relatively rare tumors are managed and analyzed carefully.

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Localization and Surgical Treatment of Occult Insulinomas

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Management of patients with biochemical evidence of insulinoma and negative preoperative imaging studies (occult) tumors is controversial, varying from primarily medical management to aggressive, blind nearly total pancreatectomy to extirpate the tumor. Since 1982, 12 consecutive patients with occult insulinoma underwent preoperative portal venous sampling (PVS) for insulin followed by surgical exploration with intraoperative ultrasound (IOUS). Eleven of twelve patients (92%) had insulinoma removed and were cured. Portal venous sampling correctly predicted the location of the insulinoma in 9 patients (75%) and that no tumor would be found in another patient. A fourfold insulin gradient in the pancreatic tail of one patient correctly predicted that a distal pancreatectomy would remove the insulinoma despite the fact that neither palpation nor IOUS identified any tumor. Intraoperative ultrasound was the single best method to identify occult tumors because it correctly identified 10 of 11 insulinomas that were found, including five pancreatic head tumors that were not palpable. Palpation identified five insulinomas. Of the 10 tumors that were identified during operation by palpation or ultrasound, IOUS identified significantly more (100% *versus* 50%, p = 0.03) and guided the successful enucleation of each. The results support the strategy of preoperative PVS and operation with IOUS to localize and remove insulinoma in patients with occult tumors. Most tumors (75%) will be correctly localized to a specific pancreatic region by preoperative PVS and identified by IOUS (83%), allowing simple enucleation and biochemical correction of hypoglycemia. Morbid blind pancreatic resections are no longer indicated and long-term medical management of hypoglycemia should be reserved for the occasional patient (8%) who fails preoperative PVS and operation guided by IOUS.

INSULINOMAS ARE THE most common islet cell tumor.[1] Because of their small size, they pose a major challenge in localization. If one excludes patients with Multiple Endocrine Neoplasia type 1, which includes only 5% of all patients with insulinomas,[2] insulinomas generally are benign (90%), intrapancreatic (nearly 100%), and solitary small neoplasms (measuring less than 2 cm).[3] Surgical enucleation or resection of insulinomas always has been the treatment of choice, and if achieved, results in cure of the hypoglycemia.[4] The major problem with insulinomas is accurate localization. When tumors are not localized, 'blind' distal, subtotal, nearly total, and/or total, pancreatectomies that also require concomitant splenectomy are recommended by many surgeons.[5-9] However these procedures are complicated by short-term morbidity (pancreatitis, pancreatic fistula, pancreatic abscess) and long-term morbidity (exocrine pancreatic insufficiency and diabetes mellitus).[5,6] The morbidity of major blind pancreatic resection, the reduced likelihood of finding the insulinoma in patients with occult tumors, and the benign nature of occult insulinomas has led some physicians to recommend medical management of the hypoglycemia with diet, diazoxide, and octreotide, and to withhold surgery unless patients are poorly controlled on medication or a tumor is identified clearly.[10] The best treatment results are obtained in patients who have accurate preoperative localization.

The diagnostic localization procedure of choice for insulinomas is selective angiography. In our experience[11] and the experience of others,[12] selective angiography has identified approximately 80% of insulinomas. However recent results indicate that fewer insulinomas are visualized accurately by angiography[13] and the incidence of patients with biochemical evidence of insulinoma and negative angiograms may be as high as 50%.[13] Other radiographic methods such as infusion computed tomography

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(CT), standard CT, ultrasound, and magnetic resonance imaging have been ineffective at localizing islet cell tumors, including these occult tumors.[10–14] If the incidence of patients with angiographically occult insulinomas is increasing, as it appears to be, then the role of surgery in the management of these patients is increasingly unclear.

In 1982, when we first began this study, two techniques were introduced that we thought might be helpful to localize occult insulinomas. Portal venous sampling (PVS) was reported and appeared promising.[15] Its potential to localize occult insulinoma had been speculated.[16] Intraoperative ultrasound (IOUS) was described[17] but its utility in localizing occult insulinomas had not been evaluated. In addition, because insulinomas are uniformly distributed throughout the entire pancreas,[18] perhaps PVS could indicate a pancreatic region on which to focus the IOUS. One of the early patients had dramatic results.[19] Portal venous sampling localized an insulinoma to the pancreatic head. At exploration the tumor was not palpable. Instead of requiring a Whipple pancreaticoduodenectomy, IOUS imaged a 8-mm insulinoma and guided the successful enucleation of it.[19] Therefore we began a prospective study to evaluate the ability of IOUS coupled with PVS sampling to localize and resect insulinomas in patients with occult insulinomas. We report here our results in 12 consecutive patients with occult insulinoma; that is, insulinomas not visualized before operation by any radiographic imaging study. The results demonstrate a remarkable degree of success at finding insulinomas in patients with occult tumors and suggest that intraoperative ultrasound is primarily responsible for the success.

Methods

Between July 1982 and January 1990, 23 patients with a diagnosis of insulinoma and without Multiple Endocrine Neoplasia Type I were eligible for the current study. Each patient had the diagnosis of insulinoma established by an inappropriate elevation of serum insulin level and hypoglycemia following a fast.[3] Factitious hypoglycemia was dismissed, as described previously.[20] Each patient had preoperative radiographic imaging studies, including ultrasound,[21] CT,[11] and selective pancreatic angiography.[11] Patients who had insulinomas visualized by any of these modalities ($n = 11$) were excluded from this study.

Twelve patients had no insulinoma localized (occult tumors) and compose the population of this study. Each patient underwent percutaneous transhepatic portal venous sampling with selective vein sampling for insulin concentrations, as described previously.[16] The insulin gradient, expressed as a percentage of the simultaneous peripheral sample, was calculated as follows: insulin gradient = 100 × [(maximal selective insulin concentration – simultaneous peripheral insulin concentration/(simultaneous peripheral insulin concentration)].[22] An insulin gradient of 50% or more was interpreted as localizing the insulinoma regionally to the head, body, or tail of the pancreas. Between 20 and 30 samples for insulin concentration were obtained from each patient with a median number of samples of 26.

Patients then underwent a trial of medical management of the hypoglycemia with frequent feedings and oral diazoxide to determine if, in the event of inability to operatively localize an insulinoma, medical management of hypoglycemia would be adequate.

All operations were performed in a similar manner. The head of the pancreas was exposed by performing an extended Kocher maneuver and the body and tail were exposed by entering the lesser sac and dividing along the inferior border of the pancreas. Systematic palpation of the entire pancreas was performed, followed by intraoperative real-time high-resolution ultrasound, as previously described.[23] Initially detailed palpation of the entire pancreas was performed and any identified abnormality was recorded. Then IOUS was performed and any abnormality identified was recorded. All abnormalities identified by palpation or IOUS were biopsied. Generally insulinomas were enucleated. Occult tumors in the pancreatic head were enucleated. Occult tumors in the body or tail were enucleated, unless they were adjacent to the pancreatic duct, in which case they were resected by a distal pancreatectomy. Blind resections of the pancreas were not performed. If an insulinoma could not be identified by intraoperative maneuvers, a pancreatic resection was performed only if an insulin gradient suggested a region to resect. Operative monitoring of blood sugar was not used as an indication to terminate the procedure and surgery was terminated if the pathologist diagnosed an islet cell tumor on frozen section or if the operation was thought to be futile.

Results of selective venous sampling, palpation, and operative ultrasound were compared to the final surgical pathologic result, as described previously.[23] Each patient was re-evaluated at least 3 months after surgery. Criteria for 'cure' (biochemical remission) of insulinoma include (1) no symptoms of hypoglycemia following a fast, (2) fasting blood glucose level more than 2.2 mmol/L (millimolar), (3) fasting serum insulin level less than 6 μU/mL, and (4) documented weight loss. Statistical comparison of proportions was performed by Fisher's exact test.

Results

Operative Tumor Localization

Eleven of twelve patients (92%) with occult insulinoma had tumors removed (Table 1). Each insulinoma was located within the pancreas. The mean diameter of these occult tumors was 1.2 cm (range, 0.7 to 2.5 cm) and the

TABLE 1. *Portal Venous Sampling and Operative Localization Maneuvers for Insulinoma Patients with Negative Preoperative Imaging*

			Preoperative PVS*	Intraoperative†		Pathology	
Patient	Sex	Age (yrs)	Site and Magnitude of Positive Insulin Gradient	Palpation	IOUS	Tumor Size and Location	Postoperative Outcome‡
1	F	29	Pancreatic tail 5150%	−	+	0.7-cm head	Cured
2	F	30	Pancreatic tail 225%	+	+	1.0-cm tail	Cured
3	F	31	Pancretic body 1358%	+	+	1.2-cm body	Cured
4	M	24	None	−	−	Not found	Not cured
5	F	54	Pancreatic tail 1348%	+	+	1.5-cm tail	Cured
6	F	30	Pancreatic tail 725%	+	+	2.5-cm tail	Cured
7§	M	34	Pancreatic tail 445%	−	−	1.0-cm tail	Cured
8	F	29	None	+	+	1.5-cm body	Cured
9	F	25	Pancreatic head 1251%	−	+	0.8-cm head	Cured
10‖	F	55	Pancreatic head 500%	−	+	1.0-cm head	Cured
11	F	34	None	−	+	0.8-cm head	Cured
12	F	25	Pancreatic head 740%	−	+	1.2-cm head	Cured

* Results of preoperative PVS for insulin were considered positive if the gradient was ≥50%.

† Intraoperative results were classified as (+) if a histologically proved insulinoma was identified or (−) if none was found.

‡ Patients were classified as cured or not cured as defined in Methods.

§ In patient #7, tumor was found by a distal pancreatectomy based on an insulin gradient in the pancreatic tail.

‖ Patient #10 previously had undergone an unsuccessful subtotal pancreatectomy.

tumors were distributed throughout the pancreas. None of the insulinomas had any pathologic features of malignancy. No patient had more than one tumor identified.

Ten patients had insulinoma accurately localized during operation, thus allowing enucleation. Five of the ten islet cell tumors found at surgery were localized by palpation, and IOUS identified each of the five tumors that were palpable and five additional tumors that were not palpable (Fig. 1). Intraoperative ultrasonography was significantly better than palpation for operative localization of occult insulinomas (5 of 10 *versus* 10 of 10 localized, p = 0.03). Each of the five tumors found only by IOUS were located in the pancreatic head (Table 1). None of these tumors would have been removed by a blind subtotal pancreatectomy, including the tumor in patient 10 who had previously undergone that procedure elsewhere.

The ultrasound appearance of an insulinoma was typically a discrete sonolucent mass lesion that was well demarcated from the surrounding pancreas (Fig. 1). One insulinoma appeared to have an echogenecity pattern similar to the surrounding pancreas, thus making it difficult to visualize; however that tumor had a clear, sonolucent rim with echogenic borders (Fig. 2). Verification of IOUS findings were confirmed by imaging in two planes and the ability to repeatedly image the same mass lesion.

Both methods of operative localization were positive in five patients. Palpation did not identify any tumors that ultrasound missed. In addition neither palpation nor IOUS had false-positive findings. One insulinoma was not identified by IOUS or palpation and was only identified by pathologic examination following a distal pancreatectomy. This procedure was based on an insulin gradient in the pancreatic tail (patient 7, Table 1, Fig. 3).

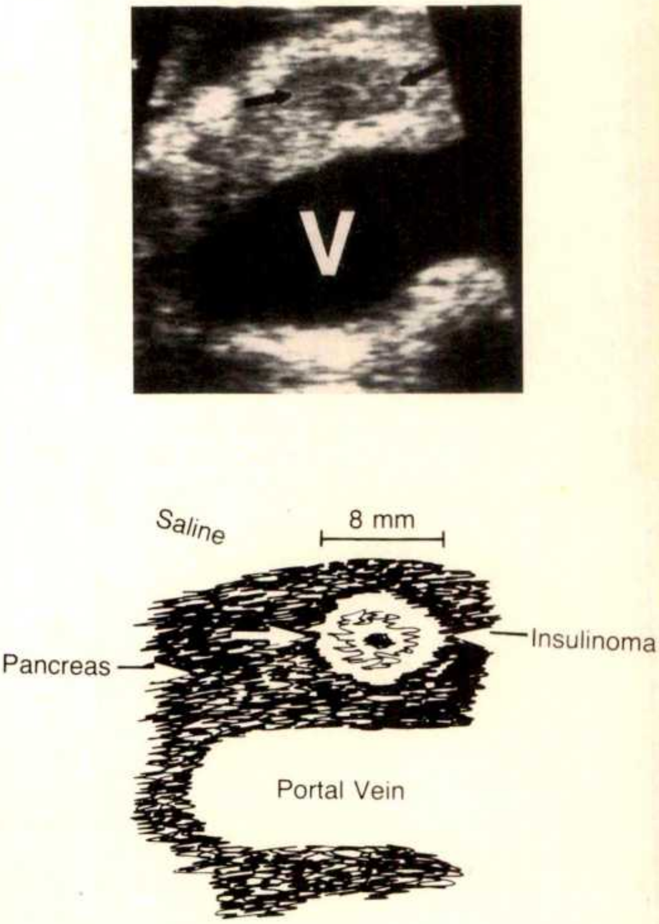

FIG. 1. A transverse IOUS scan shows a small pancreatic insulinoma (arrows) that was not palpable within the pancreatic head (patient 9). The tumor is less echo dense than the surrounding normal pancreas. This tumor measured 8 mm in diameter and was superficial to the portal vein (V) at its origin. The tumor has been dissected partially surgically and one can see saline (sonolucent) around the pancreas near the star.

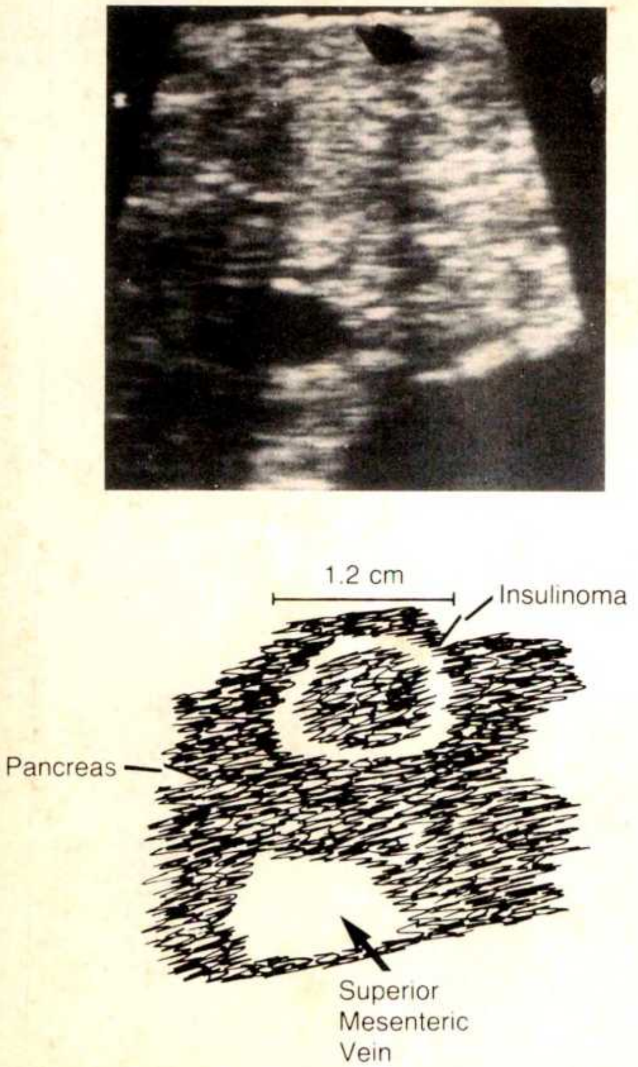

FIG. 2. A transverse intraoperative ultrasound scan shows a 12-mm pancreatic insulinoma (arrow) that was not palpable within the pancreatic head (patient 12). Unlike most islet cell tumors (Fig. 1), this tumor is not appreciably different in echo density from the surrounding pancreas. However there is a sonolucent rim around the tumor that allows it to be successfully identified by IOUS.

Selective Venous Sampling

Nine of twelve patients (75%) had a selective vein insulin gradient, and an insulinoma was found in the exact location suggested by the gradient in each patient. In the three patients without selective insulin gradients, insulinoma was removed from the body of the pancreas in one patient (number 8), the head of the pancreas in another patient (number 11), and was not found in the final patient (number 4). In one patient (number 7), the insulinoma was removed only because of PVS. In this patient PVS demonstrated a marked step-up in the pancreatic tail, but operative maneuvers, including IOUS, did not identify an insulinoma. A distal pancreatectomy was performed based on PVS and a 1-cm insulinoma was removed (Table 1, Fig. 3). In patients with occult insulinoma, PVS correctly predicted the location of the tumor in 9 of 12 patients and correctly predicted that no tumor would be found in another; therefore its results were accurate in 83% of patients, including one patient in whom tumor would not have been removed without it.

Morbidity and Outcome

Venous sampling did not result in complications in any patient. Surgical exploration resulted in significant complications in two patients. One patient required reoperation 2 months after operation for a small bowel obstruction, and another patient required reoperation for a pancreatic abscess. These complications completely resolved. No patient developed diabetes mellitus or exocrine pancreatic insufficiency. The overall complication rate was 17%. There were no therapy-related deaths.

Eleven of twelve patients had a solitary insulinoma removed and each was cured (92% cure rate). The solitary patient who had no insulinoma found has persistent hypoglycemia controlled medically by diazoxide 4 years after unsuccessful surgery.

Discussion

Greater recognition of the symptoms and signs of insulinomas combined with newer assays, including C-peptide and proinsulin levels, have led to an earlier definitive

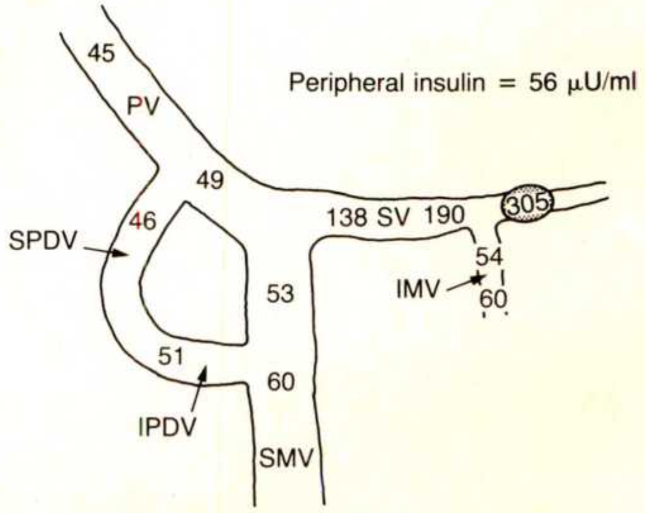

FIG. 3. Transhepatic selective venous sampling of the portal vein and its tributaries for insulin. Venous insulin levels are markedly elevated in the distal splenic vein (shaded circle, patient 7). Intraoperative ultrasound and palpation of the pancreas body and tail did not reveal an insulinoma. A distal pancreatectomy was performed based on the PVS gradient and the pathologists confirmed the presence of a 1-cm insulinoma. SPDV, superior pancreaticoduodenal vein; IPDV, inferior pancreaticoduodenal vein; PV, portal vein; SV, splenic vein; SMV, superior mesenteric vein; and IMV, inferior mesenteric vein. Insulin concentrations are given in μU/mL.

diagnosis of insulinoma.[3,4,20] Early diagnosis may have contributed to another problem in the management of these patients, inability to localize the tumor before operation. Despite the fact that many patients with insulinomas will have tumors localized by angiography,[11,12] the incidence of patients with occult insulinomas seen at the National Institutes of Health, as reported elsewhere,[13] has increased from 3 of 19 patients (16%), as reported previously[11] to 12 of 23 patients (52%), as presently reported. The management of these patients remains a difficult clinical problem.

Occult insulinomas generally are small, making localization both before and during operation difficult. If tumors are not found at exploration, surgeons have recommended blind pancreatic resection to remove the tumor along with normal pancreas.[5–7] The pancreas and spleen are removed from left to right such that more and more normal pancreas is resected. Some have recommended intraoperative monitoring of blood glucose to demonstrate a rebound hyperglycemia after removal of the pancreas with the insulinoma to document that the insulinoma has been removed.[7] Blind resections in this manner are morbid and have a 33% chance of not removing the insulinoma because some occult insulinomas will be in the pancreatic head. In fact, in the present series, 5 of 11 occult tumors (45%) were located in the pancreatic head and would have been unsuccessfully treated by blind subtotal pancreatectomy. We believe that the results of this current study indicate that blind pancreatectomy is not a reasonable strategy for patients with occult insulinoma.

Two newer localization techniques (PVS and IOUS) have changed the operative management of patients with occult insulinoma. Portal venous sampling for insulin can pinpoint reliably the exact region of the pancreas with the insulinoma in most patients. In this series it identified the region in 75% of patients. There were no false-positive results (Table 1, Fig. 3). Precise regional localization allows meticulously focused dissection of a pancreatic region and purposeful, accurate probing of a smaller area with IOUS. In the nine patients with positive regional localization by PVS, operative ultrasound localized the tumor in eight while palpation identified the tumor in only 4 patients (Table 1). Portal venous sampling identified the region on which the surgeon could focus IOUS. In the final patient with positive PVS (number 7), despite negative operative maneuvers, including IOUS to localize the insulinoma, an enlightened resection based on PVS information could be performed and was successful (Fig. 3). In addition, although PVS is an invasive procedure with needles, catheters, and guide wires traversing the liver, it has minimal morbidity. In our experience no patients with occult insulinoma had complications from PVS; and in the gastrinoma context, only 4 of 27 patients (15%) had prolonged pain after the procedure that resolved slowly on its own without treatment.[22] Portal venous sampling increases cost and requires considerable expertise by the radiologist, but if an insulin gradient is obtained, it reliably localizes the exact pancreatic region with the insulinoma. If there is no insulin gradient on PVS, surgery is still indicated because most patients (two of three) will have successful operations (Table 1).

The major breakthrough in the localization of occult insulinomas is the use of intraoperative ultrasound. It is a procedure performed jointly by the surgeon and ultrasonographer that requires each person for best results. Because insulinomas are almost always within the pancreas and the ultrasound appearance of the tumor is so different from the pancreas (Fig. 1), small, occult insulinomas can be visualized reliably by IOUS. Intraoperative ultrasonography localized significantly more occult insulinomas than palpation. It allowed the successful enucleation of five pancreatic head insulinomas that would not have been able to be removed by another surgical procedure except a morbid Whipple pancreaticoduodenectomy. Intraoperative ultrasonography was necessary to facilitate excision of these insulinomas. An incision was planned based on ultrasound determination of the shortest, most direct route to the tumor without traversing the pancreatic duct or other vital structures. After the incision was made, IOUS was performed again as the pancreas was traversed. The shortest path was continually reconfirmed by IOUS until the tumor was visualized and then an enucleation could be performed. The ability of IOUS to find insulinomas that are not palpable also has been reported by others,[24] further corroborating the utility of this instrument to operatively localize occult tumors. Therefore the advantages of the use of operative ultrasound in the treatment of insulinomas include (1) precise operative localization, (2) enucleation of nonpalpable nonvisible tumors, and (3) avoidance of ductal injuries as well as injuries to other vital structures by precise localization of adjacent vital structures such as the portal vein (Fig. 1).

The results of the present study support the strategy of portal venous sampling for insulin to localize a specific region with the insulinoma and surgery guided by IOUS to identify and remove the tumor in patients with occult insulinomas. In 12 patients managed with this strategy, small insulinomas were removed in 11 patients and each was cured (92%). This high degree of success was achieved with acceptable morbidity. Some may suggest that PVS is not absolutely necessary because it was only positive in 75% of patients and two of three patients in whom it was negative still had successful operations. We argue that it is helpful because one patient (number 7 Table 1, Fig. 3) had a successful operation primarily because of PVS. It produced no false-positive results, so one can confidently plan a pancreatic resection procedure based on an insulin gradient if no tumor is identified during exploration. The use of intraoperative ultrasound markedly improved the results because it identified significantly more insulinomas than palpation and it guided their successful enucleation.

We conclude that IOUS greatly facilitates the excision of occult insulinomas. Exploratory surgery for occult insulinomas should not be performed without the use of IOUS. The exploration for occult insulinomas should no longer rely on blind distal or subtotal pancreatectomy,[5-8] but rather on precise localization of the tumor facilitated by preoperative PVS and IOUS. Because of the high overall success rate demonstrated here, pure medical management of hypoglycemia in patients with occult insulinoma should be reserved only for the few patients (8%) in whom this strategy is unsuccessful.

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Surgical Management of Pheochromocytoma with the Use of Metyrosine

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Despite recommended preoperative preparation with alpha-adrenergic blockers, severe hemodynamic instability may occur during operations to resect pheochromocytoma. We combined the alpha-blocker phenoxybenzamine with the tyrosine hydroxylase inhibitor metyrosine in an attempt to better manage the hypertension of patients with pheochromocytoma undergoing surgical resection. This report reviews the cases of 25 consecutive patients undergoing surgery for known intra-abdominal pheochromocytoma. Each patient had elevated serum or urine levels of catecholamines or their metabolites. Nineteen patients were prepared before operation with phenoxybenzamine and metyrosine and six patients were given phenoxybenzamine alone. There were no significant differences in maximum, minimum, or mean blood pressure before or after tumor resection between patients who received metyrosine and those who did not. However careful review suggested that those who received metyrosine had more severe disease as judged by biochemical criteria. Study of selected patients matched for age and severity of disease suggested that the intraoperative blood pressure management of patients prepared with phenoxybenzamine and metyrosine was facilitated. In addition metyrosine-prepared patients lost less blood and required less volume replacement during surgery than did non-metyrosine-prepared patients. There were no apparent differences in postoperative fluid requirements. Although the study is not a prospective randomized trial, a retrospective review of patients managed with the combination of phenoxybenzamine and metyrosine suggests that surgery to resect pheochromocytoma can be better performed with both drugs than with phenoxybenzamine alone. The combination regimen appears to result in better blood pressure control, less blood loss, and the need for less intraoperative fluid replacement than does the traditional method of single-agent alpha-adrenergic blockade.

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PHEOCHROMOCYTOMA IS A rare tumor occurring in less than 0.1% of the hypertensive population.[1] Hypertension, either continuous or paroxysmal, is the most frequent manifestation of this disease and is frequently associated with episodes of sweating, headache, and tachycardia.[2] Pheochromocytoma is not infrequently associated with familial syndromes such as multiple endocrine neoplasia type II, and neuroectodermal syndromes such as neurofibromatosis and von Hippel-Lindau syndrome.[3] Pheochromocytomas occur most frequently in patients between the ages of 30 and 50 years, occur with equal frequency in both sexes, and occur less frequently in blacks.[4] Surgery is the mainstay of treatment and is the only treatment that can result in cure. Before the introduction of alpha-adrenergic antagonists for the preoperative management of pheochromocytoma, the surgical mortality rate was prohibitive, ranging from 24% to 50%.[5,6] Today with recommended preoperative preparation, the surgical mortality rate is approximately 3%.[5,6] Most commonly patients are prepared with the alpha-adrenergic blocker phenoxybenzamine (Dibenzyline, SmithKline and French, Philadelphia, PA) with or without the addition of a beta-adrenergic blocker. Despite apparently adequate preparation, severe hemodynamic instability and arrhythmias may occur during surgery. Hemodynamic instability is manifested by hypertension during induction of anesthesia and tumor manipulation, as well as profound hypotension after tumor removal.[5] Thus there is controversy about the optimum method for preparing these patients for definitive surgery.

The tyrosine hydroxylase inhibitor metyrosine (Demser, Merck, Sharp & Dohme, West Point, PA) has been used for management of patients with pheochromocytoma.[7] Since 1978 we have used routinely the combination

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of this drug and phenoxybenzamine for the preoperative preparation of most patients with pheochromocytoma, believing that the combination might decrease perioperative blood pressure instability and make the management of these patients easier and safer. We report the results in 19 patients managed with the drug combination and contrast them with the results in six patients managed with phenoxybenzamine alone. The results demonstrated no differences in maximal and minimal intraoperative blood pressure before or after pheochromocytoma resection between patients prepared with or without metyrosine. However, despite the fact that patients prepared with the drug combination had more severe biochemical changes, their operative course appeared more stable. Metyrosine-treated patients had less blood loss and required less intraoperative fluid and less medication to control blood pressure.

Materials and Methods

Patients and Workup

The data analyzed originate from 25 patients who underwent resection of intra-abdominal pheochromocytoma in the Surgery Branch of the National Cancer Institute between June 1982 and April 1989. Patients whose primary tumors were located in an extra-abdominal location, as well as one patient whose tumor was discovered incidentally, were excluded from analysis. One patient who had a large adrenal tumor had significant blood loss from an extra-abdominal procedure and therefore was excluded from the fluid balance analysis. Patients generally were admitted with the diagnosis of pheochromocytoma and commonly were taking many antihypertensive medications. These medications, with the exception of phenoxybenzamine, generally were stopped before we obtained biochemical studies to confirm the diagnosis of pheochromocytoma. The routine studies included 24-hour urine collections for catecholamines, vanillylmandelic acid (VMA), and metanephrines, and serum determinations of epinephrine and norepinephrine. The diagnosis of pheochromocytoma was confirmed if any of these studies was abnormally elevated. Imaging studies such as computed tomography (CT), magnetic resonance imaging (MRI), and I^{131} metaiodobenzylguanidine (MIBG) scan were performed to localize tumors. Arteriography and venous sampling were not performed.

Preoperative Preparation

To start we administered to the patients oral phenoxybenzamine 10 mg two times daily, increasing the dosage to an average of 0.5 mg/kg per day in two divided doses. After obtaining appropriate levels of alpha-adrenergic blockade, beta-adrenergic blockers were added to the medication regimens of those patients with persistent tachycardia. Nineteen patients also were treated with metyrosine (Demser) at an initial dosage of 250 mg every 6 hours (given orally). This dosage was increased 250 to 500 mg daily, as necessary, to a maximum dosage of 4 g per day. One or two weeks of metyrosine treatment were required for adequate patient preparation, as judged by the absence of symptoms, normalization of blood pressure and pulse, and the presence of only mild (less than 20 mmHg) orthostatic hypotension. Frequently the total dose of phenoxybenzamine could be reduced after the addition of metyrosine. At 12:00 A.M. on the day of surgery, the patient was given 1 mg/kg of phenoxybenzamine and 1 g of metyrosine orally with a sip of water.

Most patients were premedicated with an oral dose of benzodiazepine 1 to 1.5 hours before surgery. Atropine was not ordered because of potential tachycardia, central nervous system stimulation, and potentiation of vasopressor activity of catecholamines. Generally narcotics with histamine-releasing properties also are contraindicated.

Anesthesia

When the patients were brought to the operating room, patients were equipped with monitoring devices, including an electrocardiograph, a temperature probe, a precordial stethoscope, an automatic blood pressure cuff, an end tidal capnograph, and pulse oximetry. Two large-bore peripheral intravenous catheters and an arterial blood pressure monitoring line were inserted before induction of anesthesia. A central venous pressure or pulmonary artery catheter was inserted in each patient, in most cases following the induction of anesthesia. All patients received general endotracheal anesthesia. Induction was accomplished with a combination of sodium thiopental, fentanyl, and enflurane or isoflurane in 100% oxygen. A slow, smooth, hemodynamically stable induction was preferred. Intubation was facilitated with succinylcholine, pancuronium, or vecuronium. Intravenous lidocaine was used to attenuate hypertensive and tachycardic responses to laryngoscopy and intubation. After intubation a Foley catheter and nasogastric tube were inserted. General anesthesia was maintained with oxygen, nitrous oxide, enflurane or isoflurane, fentanyl, and pancuronium or vecuronium. In addition to deepening anesthesia, nitroprusside and/or phentolamine were used as needed to control hypertension, and propranolol was used to control tachycardia. Arterial blood gas determinations were monitored serially to detect potential life-threatening lactic acidosis.[8] Episodes of hypertension were not infrequent during induction of anesthesia, tracheal intubation, and surgical manipulation of the tumor. With ligation of the tumor's venous drainage, hypotension, if present, was treated with vigorous saline replacement. Vasopressors were avoided whenever possible. After completion of surgery, each patient remained intubated and was transferred to the intensive care unit. Positive pressure mechanical ventilation was instituted and each patient was allowed to emerge slowly from the anesthetic.

Operative Approach

The anterior approach was chosen in all patients to allow for careful palpation and examination of extra-adrenal sites such as the periaortic and pericaval ganglia as well as the contralateral adrenal. The type and location of the incision was chosen by the operating surgeon based on the patient's body habitus and the size and location of the tumor. The tumor was resected by carefully ligating the surrounding tissue with hemoclips or suture material. The adrenal vein was ligated separately whenever feasible.

Following resection of the tumor, intraoperative evaluation of other potential tumor sites was accompanied by careful monitoring of blood pressure. Theoretically blockade might be so complete that manual palpation in search of an additional tumor would not produce a detectable increase in blood pressure. However, in our experience, this was not the case.

Postoperative Management

Strict attention was paid to fluid management by careful monitoring of central venous or pulmonary capillary wedge pressure. Blood pressure was supported generally by the use of vigorous fluid replacement rather than the use of vasopressors.

Statistics

Results are presented as the mean ± standard error of the mean. Individual group means were compared using the Wilcoxon rank sum test. All p values reported are two sided.

TABLE 1. *Presenting Symptoms and Signs of the 25 Patients with Pathologically Proved Pheochromocytoma*

Symptom/Sign	Number (%)
Hypertension	20 (80)
Headache	16 (64)
Diaphoresis	12 (48)
Palpitations	8 (32)
Nervousness/anxiety	7 (28)
Glucose intolerance	7 (28)
Weight loss	5 (20)
Nausea/vomiting	4 (16)
Fatigue	4 (16)
Weakness	3 (12)

TABLE 2. *Biochemical Data Consistent with the Diagnosis of Pheochromocytoma in These Patients*

Assay	Normal Range	Patient Results Mean (range)
Urine		
Catecholamines	<150 mg/24°	797 (101–2705)
VMA*	<6.8 mg/24°	21.1 (4.9–68.8)
Metanephrines	<1.3 mg/24°	9.0 (0.8–39)
Serum		
Epinephrine	<100 pg/mL	387 (0–2126)
Norepinephrine	<500 pg/mL	3918 (54–32,324)

*VMA, vanillylmandelic acid.

Results

Patient Characteristics, Symptoms, Diagnosis, and Medications

The 25 patients included 6 men and 19 women. Twenty-two patients were white and three patients were black. The mean age was 39.6 years (range, 16 to 74 years). Twenty-one patients (84%) presented with primary disease, 3 patients (12%) presented with locally recurrent disease, and 1 patient (4%) presented with metastatic disease. Seventeen patients (68%) presented with sporadic pheochromocytoma. There were 8 patients (32%) who presented with pheochromocytoma associated with various familial syndromes, including 2 patients with MEN-II, 2 with von Hipple-Lindau syndrome, 1 patient with neurofibromatosis, and 3 patients with simple familial pheochromocytoma.

The most common symptoms were hypertension, headache, diaphoresis, and palpitations (Table 1). Nearly all patients were taking antihypertensive medication, most commonly phenoxybenzamine (60%). Three patients were insulin-dependent diabetics. The overall results of the biochemical studies were consistent with the diagnosis of pheochromocytoma (Table 2).

All patients received phenoxybenzamine. The average dose was 28 mg/day (range, 10 to 60 mg/day) and the mean duration of therapy was 15 days (range, 1 to 35 days). Nineteen of these 25 patients received metyrosine, with the average dose of 833 mg/day (range, 500 to 1500 mg/day) and the mean duration of 10 days (range, 4 to 21 days). The six patients who did not receive metyrosine included five patients with 'mild' disease and one 74-year-old patient thought to be at increased risk of the central nervous system complications from metyrosine. Six patients required additional preoperative medications: beta-adrenergic blockers (propranolol, atenolol) in five patients and the alpha-adrenergic blocker prazosin in one patient.

TABLE 3. *Operative Findings During Resection of Pheochromocytoma in 25 Patients*

Operative Findings	Familial Patients Number (%)	Sporadic Patients Number (%)	Total Number (%)
Adrenal			
Unilateral	4 (50)	12 (70.6)	16 (64)
Bilateral	3 (37.5)	1 (5.9)	4 (16)
Extra-adrenal			
Retroperitoneal	1* (12.5)	3 (17.6)	4 (16)
Bladder		1 (5.9)	1 (4)
Total	8	17	25

* Multiple sites.

Operation

Each patient underwent surgery *via* an abdominal approach. The incision was a bilateral subcostal incision in 11 patients, a midline incision in 8 patients, and a thoracoabdominal incision in 6 patients. The pheochromocytoma was within the adrenal in 20 patients. The tumor was unilateral in 16 patients and bilateral in four patients (Table 3). Bilateral disease was observed in three patients who had a family history of pheochromocytoma and in one patient with sporadic disease. The remaining five patients had extra-adrenal pheochromocytomas with four tumors localized to the retroperitoneum and one within the bladder. Four patients required additional procedures to excise their tumors, including one nephrectomy, one wedge liver resection, and one excision of a portion of the diaphragm. There were 7 patients who underwent 10 additional procedures unrelated to the removal of the pheochromocytoma itself and included 2 liver biopsies, 1 enucleation of 1 gastrinoma,[9] and 1 pancreatic exploration. The median operating time was 270 minutes, and there was no significant difference between the metyrosine and nonmetyrosine groups.

The final pathologic diagnosis was pheochromocytoma in all 25 patients. Grossly tumors generally were encapsulated. They frequently showed cystic change and had a tan-red soft-cut surface. The tumors ranged in size from 4 mm to 15 cm in greatest diameter (mean 5.7 cm). Histologically all tumors exhibited characteristic features of pheochromocytoma with a 'zellenballen' growth pattern. Capsular invasion was demonstrated in one case, and vascular invasion in three cases.

Hemodynamics and Fluid Requirement as a Function of Medication

Hemodynamic data from the operating room are divided into subgroups based on whether a patient received metyrosine before operation. There were no apparent differences in intraoperative blood pressure measurements recorded in patients receiving metyrosine compared to those who did not (Table 4). However patients in the metyrosine group appeared to have more severe disease as judged by higher serum and urinary catecholamines (Table 5), but the differences were not statistically significant. Although the metyrosine-treated patients appeared to have more severe disease, they did as well hemodynamically as patients with less severe disease who were treated with phenoxybenzamine alone. A comparison was made between four representative patients in the metyrosine and non–metyrosine-treated groups selected for age, severity of disease, and type of operation. As is apparent, the metyrosine-treated patients had a more stable intraoperative course with less fluctuation of blood pressure (Fig. 1).

Of the 19 patients in the metyrosine group, 12 patients (63%) required intraoperative blood pressure medications (10 needed anti-hypertensive medication and 2 first needed antihypertensive medication and later vasopressors). Of the 6 patients in the non–metyrosine-treated group, 5 patients (83%) required intraoperative blood pressure medications (3 needed antihypertensive agents and 2 needed vasopressors). The difference between the two groups was not statistically significant. Of the subgroup of six metyrosine-treated patients requiring additional antihypertensive agents to control their symptoms and blood pressure before operation, only 1 patient (17%) required additional blood pressure medication during operation. Thus the degree of difficulty of controlling the

TABLE 4. *Operating Room Hemodynamic Data During Resection of Pheochromocytoma in 25 Patients*

		Before Tumor Out		After Tumor Out
Preparation	n	Maximum BP (range)	Minimum BP (range)	Average BP (range)
With metyrosine*	19	190/108 ± 8/6 (140/76–270/150)	89/49 ± 3/2 (70/40–105/60)	115/68 ± 2/3 (95/48–130/88)
Without metyrosine*	6	174/90 ± 17/12 (130/70–210/110)	83/46 ± 6/4 (65/45–90/60)	105/64 ± 5/3 (88/48–120/73)

* All patients received phenoxybenzamine.
BP, blood pressure.

TABLE 5. *Comparison of Disease Severity as a Function of Preoperative Preparation Regimen*

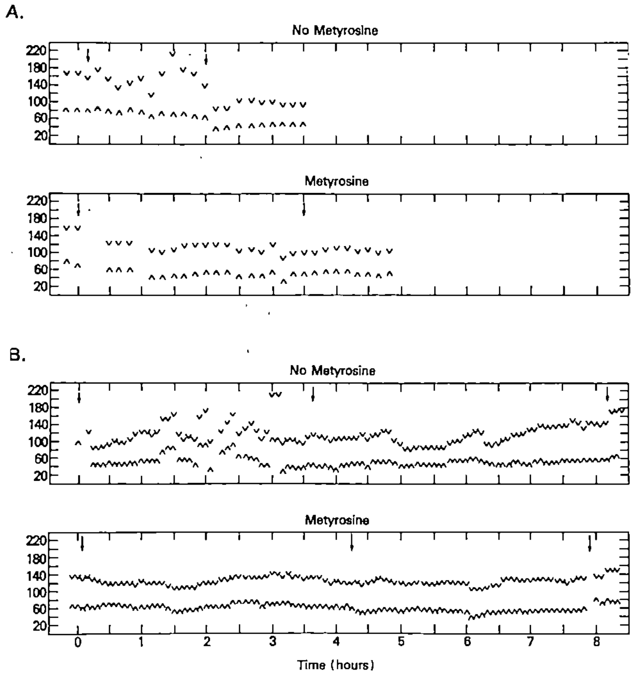
Preoperative Preparation	n	Age (years)	Serum (pg/mL)		Urine (mg/24 hr)		
			Epi	Norepi	Catechol	VMA	MN
With metyrosine*	19	39.8 ± 2.7 (16–61)	432 ± 148 (0–2126)	4770 ± 1824 (537–32,324)	1937 ± 1129 (202–13,105)	20.6 ± 3.9 (4.9–39.7)	9.0 ± 3.7 (0.8–39.0)
Without metyrosine*	6	39.0 ± 8.0 (17–74)	269 ± 110 (0–1449)	1915 ± 958 (54–5790)	494 ± 196 (101–700)	10.9 ± 4.2 (4.9–22.7)	3.9 ± 1.7 (0.8–9.3)

* All patients received phenoxybenzamine.

Epi, epinephrine; Norepi, norepinephrine; Catechol, catecholamines; VMA, vanillylmandelic acid; MN, metanephrines.

blood pressure before operation did not predict the degree of hemodynamic instability during operation.

Intraoperative blood loss and fluid requirements as well as the fluid requirements for the first 48 hours after operation were analyzed (Table 6). Patients treated with metyrosine lost significantly less blood (p = 0.03) and required significantly less fluid replacement during operation (p = 0.03) than did those not treated with metyrosine. The postoperative fluid requirements were not significantly different between the two groups.



FIGS 1A and B. Four patients, two each from the metyrosine- and non-metyrosine-treated groups were matched as closely as possible for clinical factors (age, degree of biochemical function, size of tumor, and type and extent of operation). (A) Metyrosine-treated patient exhibited smoother intraoperative course. Patients differed in that non–metyrosine-treated patients were older (74 *vs.* 50 years) but the metyrosine-treated patient had a larger tumor (10 cm *vs.* 5 cm). (B) Metyrosine-treated patient exhibited smoother intraoperative course. Patients differed in that the non–metyrosine-treated patient had a larger tumor (10 cm × 8 cm *vs.* 3 cm) but the metyrosine-treated patient had higher plasma catecholamines (NE 1262, E 52 *vs.* NE 910, E 0). (Arrows: 1st, induction; 2nd, tumor removed; 3rd, reversal of anaesthesia (if done).

There were no surgically related deaths in this group of patients. In one patient pheochromocytoma completely surrounded the left renal artery and safe removal of the pheochromocytoma required removal of the kidney. There were no major postoperative complications. The average duration of postoperative ileus was 4.5 days (range, 3 to 8 days) and there was no significant difference between the metyrosine- and non–metyrosine-treated groups. One patient did require pressor support despite significant fluid resuscitation for the first 48 hours after surgery. Three patients were hypertensive in the postoperative period, two because of fluid overload, one because of underlying essential hypertension.

Discussion

Remarkable advances have been made in the management of pheochromocytoma since the tumor was first successfully removed in 1926 by Roux of Switzerland and Mayo of the United States. Before the introduction of alpha-adrenergic blockers, the perioperative mortality rate was high, approaching 50% in some series.[5,6] Since the introduction of alpha-blockers, mortality rates now range between 0% and 3%. Consequently most groups routinely use alpha-blockers, such as phenoxybenzamine, in the preoperative management of these patients. The indications for use of beta-blockers, such as propranolol, are controversial. They are used routinely by certain groups,[10] but most groups use them only when necessary to control tachycardia and prevent arrhythmias.[2] Beta-blockers should be added only after adequate alpha-blockade is achieved.

Although good management is usually possible with phenoxybenzamine, these patients are still prone to hemodynamic instability manifested by hypertension, particularly during tumor manipulation, and hypotension after tumor removal. Although it has been suggested that blood volume can be returned entirely to normal by treating patients before operation with phenoxybenzamine,[11] large volumes of fluid replacement still are frequently required.[12] Thus we decided to investigate the effect the addition of metyrosine would have on hemodynamic stability as well as on perioperative fluid requirements. We

TABLE 6. *Blood Loss/Fluid Requirements as a Function of Preoperative Metyrosine Treatment*

		Operating Room				Postoperative					
			Replacement			First 24 Hours			Second 24 Hours		
	Number	EBL†	Crystalloid	Colloid	Blood	Crystalloid	Colloid	Blood	Crystalloid	Colloid	Blood
With	18‡	487 ± 95§	4533 ± 667§	478 ± 124	240 ± 122	2680 ± 249	285 ± 118	229 ± 71	2947 ± 296	29 ± 29	87 ± 51
metyrosine*		(200–1800)	(2300–14500)	(0–1750)	(0–2000)	(1560–5420)	(0–1500)	(0–695)	(178–5512)	(0–500)	(0–685)
Without	6	1098 ± 205	7275 ± 1145	867 ± 505	708 ± 254	2414 ± 371	821 ± 383	100 ± 100	3072 ± 82	125 ± 125	125 ± 125
metyrosine*		(250–1700)	(3600–10200)	(100–3250)	(0–1500)	(1670–3963)	(0–2300)	(0–500)	(2920–3282)	(0–500)	(0–500)

* All patients received phenoxybenzamine.

† EBL, estimated blood loss.

‡ Patient with a large adrenal tumor who suffered significant blood loss from an extra-abdominal procedure was excluded from this analysis.

§ $p < 0.05$ compared to no metyrosine.

found no significant differences in the maximum, minimum, or mean blood pressure before or after tumor removal between the metyrosine- and non–metyrosine-treated groups (Table 4). However the metyrosine-treated patients were more stable, requiring intraoperative antihypertensive medications or pressor agents less frequently than the non–metyrosine-treated group. These results are remarkable in that only those patients with minimally functioning pheochromocytomas or the elderly were included in the non–metyrosine-treated group (Table 5).

Another indicator of intraoperative hemodynamic instability is the amount of blood loss and the intraoperative fluid requirements. Again there was a significant advantage shown by the metyrosine-treated group, these patients having significantly less blood loss and requiring less fluid replacement than the non–metyrosine-treated group (Table 6). Matching of patients between the two groups as to age, severity of disease, and type of operation illustrates the advantage of using metyrosine (Fig. 1). The postoperative fluid requirements were nearly the same in both groups (Table 6) and were frequently large, which was shown previously.[12] This may be due to the extent of the operative dissection with major third space losses, a residual fluid deficit despite adequate preoperative blockade, as well as residual alpha-adrenergic and catecholamine synthesis blockade. Because the half-life of both phenoxybenzamine and metyrosine is approximately 12 hours, 30 to 36 hours is required for blood pressure autoregulation to return.[12]

There have been few previous reports on the use of metyrosine for the perioperative management of patients with pheochromocytoma.[7] Metyrosine has been used successfully for the perioperative management of a patient refractory to phenoxybenzamine and intravenous phentolamine,[13] and in a patient with severe bronchopneumonia and cor pulmonale due to chronic obstructive pulmonary disease.[14] However hypertensive crisis can still occur when metyrosine is used without concomitant alpha-blockade due to the massive release of catecholamines previously synthesized and stored.[15] Although several series include a few patients managed with metyrosine, this series represents the first large group of patients in which metyrosine and phenoxybenzamine were used routinely for the preoperative preparation of patients with pheochromocytoma.

Although we found metyrosine useful in the management of patients with pheochromocytoma, it is not indicated for all patients. It is not necessary to treat with metyrosine patients who have minimal or no symptoms from a minimally functioning pheochromocytoma. In addition usually we do not treat patients who are older than 65 with metyrosine because side effects are more common in these patients. Common side effects include sedation, vivid or frightening dreams, altered behavior, and diarrhea. It also can produce extrapyramidal symptoms, including Parkinsonism, in older patients. All these symptoms disappear rapidly when the drug dosage is reduced or stopped. None of the patients in this series required a reduction in the dosage of metyrosine because of symptoms. However several patients required a decrease in dosage when both phenoxybenzamine and metyrosine were used because of severe orthostatic hypotension.

Virtually all anesthetic agents have been used at some time with success in these patients.[16,17] However, in addition to nitrous oxide, enflurane (Ethrane, Anaquest, Madison, WI) and isoflurane (Forane, Anaquest) are the preferred inhalation agents because they do not sensitize the myocardium to epinephrine-induced dysrhythmias to the same extent as halothane (Fluothane, Wyeth-Ayerst, Philadelphia, PA). Fentanyl and sufentanyl are the preferred narcotics, and pancuronium and vecuronium are the preferred muscle relaxants because these drugs do not elicit histamine release, which may provoke tumor secretion of catecholamines. Although we chose general anesthesia for all our cases, regional anesthesia also has been described.[18]

We and most other groups,[5,10,19,20] use the transabdominal approach for patients with pheochromocytoma. This permits careful examination and palpation of the contralateral adrenal and extra-adrenal sites such as the organ of Zuckerkandl, particularly important in those with familial syndromes. The type of incision chosen should be based on the predominant site of disease as localized by preoperative imaging studies and the patient's body habitus. We generally favor a long mid-line incision for the slender patient with a high costal margin, and a bilateral subcostal or chevron-shaped incision for most other patients. For those patients with a large mass localized to one side, a thoracoabdominal approach should be considered. Recently it was suggested that because of the ability of imaging studies to localize pheochromocytoma, the flank or the posterior approach should be considered in patients with nonfamilial varieties of pheochromocytoma.[21] These results will need to be confirmed prospectively before such an approach can be recommended.

Other large centers do not use metyrosine and report equally good results. The Mayo Clinic reported a 3.8% mortality rate in 106 patients, all but eight of whom were pretreated with phenoxybenzamine and propranalol.[10] One of the four deaths was in a patient with an undiagnosed pheochromocytoma who received no preoperative blockade. In a series of patients from the M. D. Anderson Hospital,[20] no major complications were noted in 32 patients who were prepared before operation with adrenergic blockers. Severe hypertension and two deaths were noted in patients who were not prepared with alpha-adrenergic agents before surgery or arteriography. Another group showed that the selective postsynaptic alpha-1 blocker prazosin can be used with results equivalent to phenoxybenzamine in terms of perioperative fluid requirements and intraoperative hemodynamic stability.[22] Another series of 51 patients who were treated with phenoxybenzamine showed a smoother perioperative course compared to historical controls.[23] Thus it is possible to achieve good results by the use of phenoxybenzamine, phenoxybenzamine with beta blockers, prazosin or, as we have demonstrated, with phenoxybenzamine and metyrosine. Regardless of the method chosen, the patient should be prepared for a minimum of 7 to 10 days to allow for reconstitution of circulating blood volume as well as normalization of blood pressure (with mild orthostatic hypotension) and amelioration of symptoms, although recently it was suggested that a 4-to-7-day period of preparation is adequate.[24]

Pheochromocytoma is frequently associated with other familial syndromes, as seen in our series. In addition associated gallbladder disease has been described in patients with pheochromocytoma. In a previous Mayo Clinic series, approximately 29% of patients were found to have cholelithiasis and gallbladder disease.[25] However, in our series, only one patient had a history of gallbladder disease, for which she had undergone a cholecystectomy. This may be the result of increased awareness of the syndrome, with consequent earlier diagnosis of pheochromocytoma before the development of gallbladder disease. Only three patients (12%) had insulin-dependent diabetes mellitus and only two patients (8%) had significant cardiac disease.

Two patients presented particularly interesting management challenges. One patient was a 61-year-old man with a massive pheochromocytoma of the right adrenal gland who had two unsuccessful exploratory operations at other institutions. At the time of his operation, a left femoral cutdown was performed and cardiopulmonary bypass equipment was made available in case it was needed during the operation (it was not). Using a large right thoracoabdominal incision, the mass was successfully excised *en bloc* with a small wedge of liver and a small portion of the vena cava. He had an uneventful postoperative recovery.

The other patient was a 34-year-old white man who presented with hypertension, lung metastases, and left supraclavicular adenopathy from a left perirenal malignant pheochromocytoma. After treatment with cyclophosphamide, vincristine, and dacarbazine on an experimental protocol,[26,27] he showed marked improvement of his performance status and complete resolution of his pulmonary and lymph node metastases. Subsequently he underwent successful resection of his primary lesion. His disease recurred 1 year later with an isolated pulmonary metastasis that was successfully resected. Three years after his original operation he developed progressive disease and failed to respond to treatment with additional chemotherapy. Although this patient appears to have derived some benefit from this approach, it is uncertain if this innovative regimen of aggressive chemotherapy combined with surgical resection of residual disease will prove beneficial for patients with metastatic pheochromocytoma.

Thus adequate preoperative preparation is essential to minimize the surgical morbidity and mortality rates in patients with pheochromocytoma. We obtained excellent results using metyrosine with phenoxybenzamine for preoperative preparation. Metyrosine-treated patients suffered less blood loss and required less intraoperative fluid replacement than did non–metyrosine-treated patients. With proper preoperative preparation, the surgical morbidity and mortality rates for pheochromocytoma should be low.

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Does Carotid Restenosis Predict an Increased Risk of Late Symptoms, Stroke, or Death?

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The identification of carotid restenosis as an unexpected late complication of carotid endarterectomy has prompted concerns regarding its importance as a source of new cerebral symptoms, stroke, and death. To investigate these concerns, we analyzed a consecutive series of 507 patients undergoing 566 carotid endarterectomies, each documented as technically satisfactory. Postoperative duplex Doppler examination data at 3 days, 1, 3, 6, 12 months, and annually thereafter in 484 arteries (85.5%) permitted classification of these arteries according to the most severe degree of postoperative stenosis: normal (n = 306); 1% to 19% (n = 89); 20% to 50% (n = 40); more than 50% (n = 49, including 8 occluded). The incidence of more than 50% restenosis was 14.5% in female and 7.7% in male patients (p = 0.003). Life table analyses to 10 years revealed a significantly greater life expectancy among those with restenosis (p = 0.05). Stroke was also less likely in patients with restenosis, although this difference did not reach statistical significance. When survival and stroke were both endpoints, the likelihood of patients with more than 50% restenosis remaining alive and stroke free was also greater than the less than 20% stenotic group (p = 0.03). Thus patients with carotid restenosis were less likely than patients with normal postoperative scans to have late symptoms, stroke, or early death.

CAROTID ENDARTERECTOMY WAS considered a very durable procedure from its introduction in 1951 until the 1977 report by Stoney and String[1] that indicated a 1.6% recurrent operation rate in a very large and long clinical experience. Subsequent reports by others further documented recurrent symptoms in 0.6% to 3.6% of patients undergoing endarterectomy.[2-5] However the availability of noninvasive vascular laboratory techniques, and particularly the duplex scanner, provided data indicating a much higher incidence of recurrent stenosis of the carotid bifurcation. Since 1980 many studies have documented significant recurrent stenoses ranging from 6.7% to 23.9% of patients after 'successful' carotid endarterectomy.[6-24] Concerns about the potential of recurrent stenosis for the subsequent development of cerebral symptoms or carotid occlusion stimulated frequent postoperative reassessment of patients following carotid endarterectomy in many vascular surgical centers. While most published studies do not include completion operative angiographic or ultrasonic documentation of the technical adequacy of the procedure, thus raising the question of residual rather than recurrent lesions, our own report, which included such control studies, revealed a 9% significant restenosis rate.[13] The importance of intraoperative controls also has been emphasized by Barnes[19] and Sanders.[23] This report summarizes our experience with a larger group of patients in whom carotid endarterectomy was technically successful as documented by single-plane completion angiography, and in whom restenosis was carefully documented. The implication of carotid restenosis in the subsequent development of transient ischemic symptoms, stroke, and death was analyzed.

Subjects and Methods

The charts of all patients undergoing carotid endarterectomy at the Scripps Clinic and Research Foundation from July 1, 1979, to June 30, 1987 were reviewed. Selected demographic and clinical data were entered into a vascular registry. These patients were asked to return for routine clinical and vascular laboratory follow-up examinations 1, 3, 6, and 12 months after operation, and annually thereafter. Data from each follow-up visit, including both clinical and vascular laboratory information,

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also were entered in the vascular registry. Patients in whom no postoperative vascular laboratory data were available were excluded from further analysis.

All patients were evaluated by both the ATL 600 Duplex Scanner (Advanced Technology Laboratories, Bothell, WA) and the Carolina Medical Electronics Dopscan 1050 continuous wave Doppler (Carolina Medical Electronics, King, NC) with spectral analysis, and were classified as to the degree of stenosis at the carotid bifurcation. The outputs of both duplex scanners were fed into spectrum analyzers and classified as previously described by Thomas[25] and Zierler.[10] A normal duplex scan was defined as having a peak frequency up to 4 kHz and a narrow band of frequencies during systole, with a clear area beneath the systolic peak. Minor stenoses (1% to 19%) were diagnosed with mild spectral broadening or widening of the frequency band, particularly in late systole. With peak systolic frequencies above 4 kHz and increasing spectral broadening, classifications of 20% to 49% and 50% to 99% stenosis were made. Failure to obtain any internal carotid artery flow signal was classified as occlusion. In our laboratory this classification system has been compared with formal contrast angiography in 258 arteries, with a 90% sensitivity rate for detecting lesions of 50% to 99%, and an overall accuracy rate of 86%.[25]

All data were statistically analyzed with the VAX computer system of the General Clinical Research Center of the Scripps Clinic using CLINFO-Plus software, version 1.5. Gehan's Wilcoxon test was used to statistically compare data between groups.[26] The Kaplan–Meier product limit method was used to create the life table analyses and the standard errors of individual data points were generated.[27] Specific factors subjected to analysis included late postoperative hemispheric transient ischemic attacks, amaurosis fugax, stroke, survival, age, gender, diabetes, smoking, use of carotid patch, unilateral *versus* bilateral operations, reoperation, time to worst stenosis, regression of stenosis, and clinical indication for surgery. P values between groups were obtained using Peto and Peto's Long Rank tests. Chi square contingency tests were analyzed using Pearson's chi square tests.

Results

The total carotid endarterectomy experience from 1979 to June 30, 1987 included 566 operations in 507 patients. Follow-up noninvasive laboratory data were available concerning 484 operations in 430 patients (85.5%) who comprised the study group. Male patients represented 64% of the patient population. Patients who smoked comprised 76.4% of the population, and 12.4% of the patients had diabetes. The mean duration of follow-up was 41.9 months (range, 1 to 119 months). Unilateral endarterectomy was performed in 376 patients and staged bilateral procedures were done in 54. There were seven operative deaths (1.4%), three of which occurred after subsequent additional vascular or cardiac surgical procedures. Seven patients (1.4%) suffered operative strokes with permanent deficits. Nine patients were subjected to late reoperation in the same carotid bifurcation (10 operative procedures), and all of these were associated with myointimal hyperplasia. In seven of these cases (in six patients), the indication for reoperation was the onset of new symptoms, and in three others the indication was progressing restenosis, estimated at 90% or more by both duplex scan and selective angiographic criteria.

Carotid Restenosis

The carotid bifurcations were classified as normal in each postoperative duplex scan in 306 of the 484 arteries followed (63.2%). In 49 arteries a lesion characterized as more than 50% restenosis was documented at some time following carotid endarterectomy (10.1%), usually in the area of the previous endarterectomy, and these will be referred to as the 'restenosis group.' Of these 49 arteries, eight vessels were occluded. Each of these patients had a normal duplex exam in the hospital before discharge at the time of carotid surgery. Twenty-five of 311 male arteries (8%) and 24 of 173 female arteries (13.9%) developed restenosis or occlusion ($p = 0.003$). Lesions measuring between 20% and 50% were identified in 40 other arteries (8.3%), and lesions characterized as 1% to 19% were identified in 89 arteries (18.4%).

The median time for the appearance of more than 50% restenosis was 4.6 months. The mean time to reach the maximum observed level of restenosis was 12.3 months. There was no significant predilection for restenosis to occur in any age group.

Survival

When Kaplan–Meier life table analyses were performed by grouping the patients by the presence of 0% to 19% stenosis as compared with more than 20%, the group with more than 20% stenosis had a greater life expectancy ($p = 0.017$). When further stratification was done, and those with more than 50% lesions were separately identified, they, too, had a greater life expectancy than the group without evidence of restenosis ($p = 0.05$) (Fig. 1).

Stroke

When late ipsilateral stroke was analyzed as an endpoint, the probability of remaining stroke free was greater in those patients with more than 50% restenosis than in the group with less than 20% carotid stenotic lesions ($p = 0.19$, not significant [NS]) (Fig. 2). A comparison of male and female patients indicated no difference in the

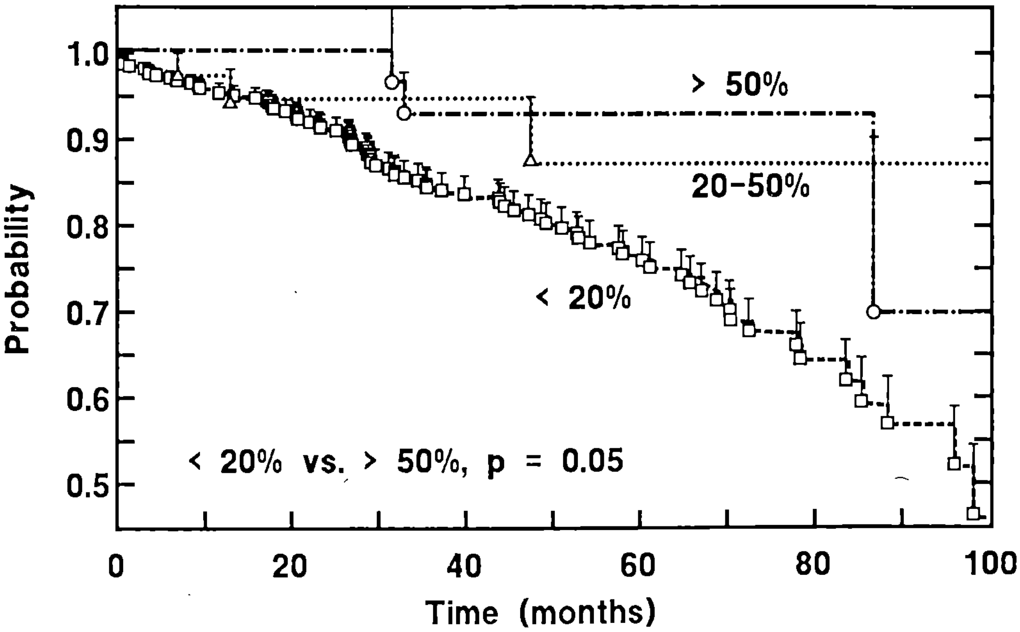


FIG. 1. Life table analysis of the effect of varying degrees of carotid restenosis on the probability of survival after carotid endarterectomy. Patients with restenosis lived longer.

likelihood of subsequent stroke, with or without the development of restenosis.

When death and stroke were combined as endpoints, the difference between the restenosis group and the normal postoperative group was more significant (p = 0.03) (Fig. 3). Finally, when transient symptoms including amaurosis fugax and hemispheric transient ischemic attacks were combined with stroke and death as endpoints, the likelihood of symptom-free survival was greater in those patients with any degree of restenosis than those who remained normal (p = 0.08, NS). Specifically, when those patients with significant degrees of stenosis (more than 50%) were compared with the intermediate (20% to 50%) and the 0% to 19% groups, the likelihood of any neurologic event was less in the severe restenosis group (p = 0.1, NS) (Figs. 4A and B). Further analysis of those patients revealed no significant difference in outcome based on sex.

In 80 of the procedures, a patch closure, usually 3 to 5 mm in width, was performed at the time of carotid endarterectomy. In general patching was used selectively for small arteries, especially with high internal carotid incisions, and particularly in female patients, because of their

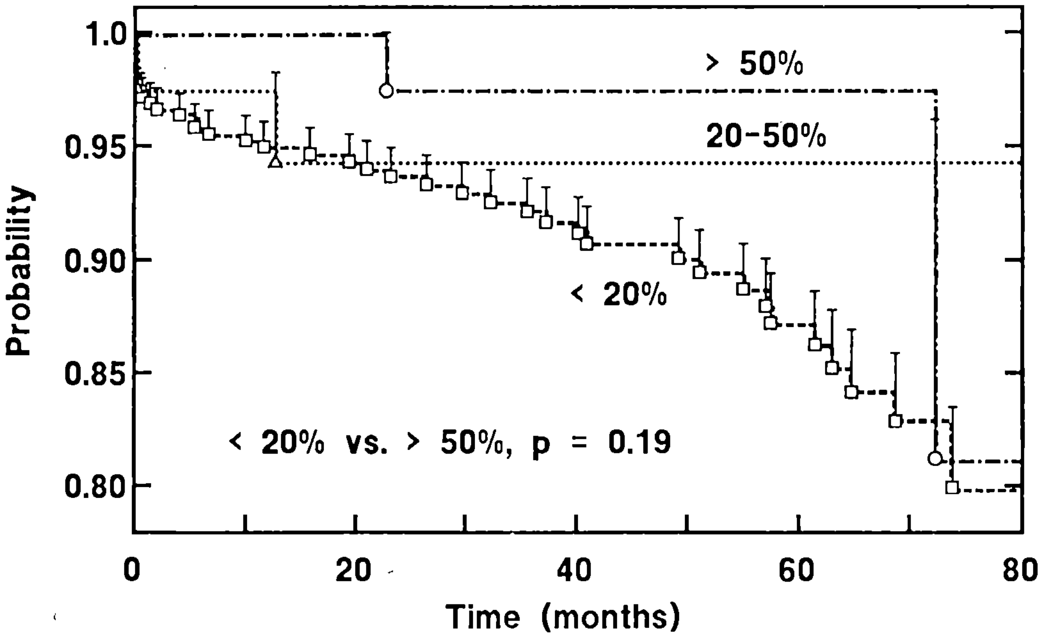


FIG. 2. Analysis of the effect of carotid restenosis on the probability of remaining free of stroke following carotid endarterectomy. Patients with restenosis were less likely to suffer subsequent stroke than those with persistently normal vessels.

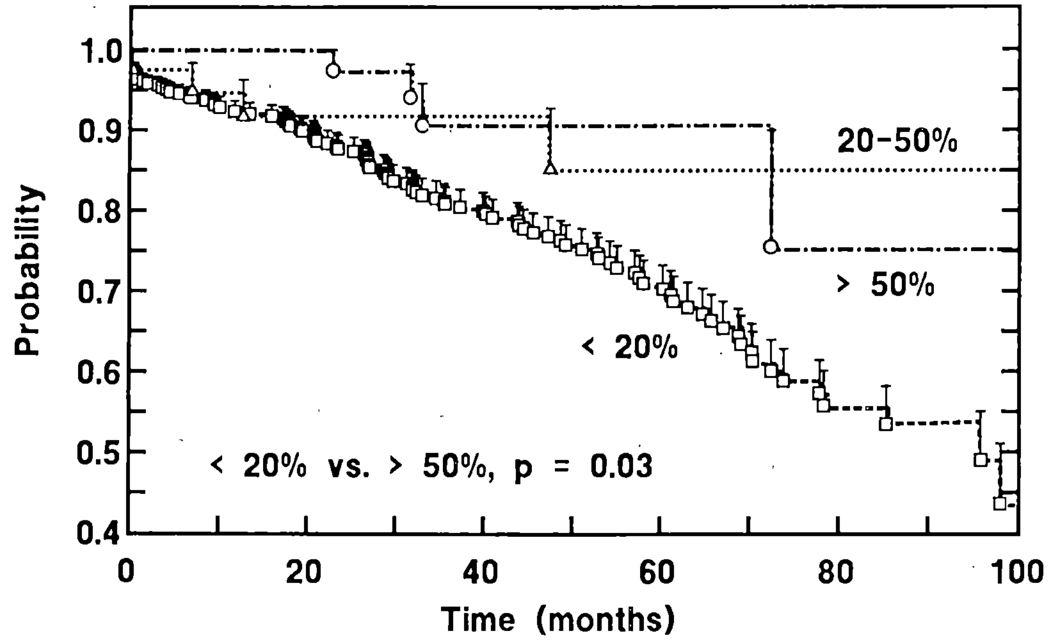


FIG. 3. Effect of carotid restenosis on the probability of remaining alive and stroke free.

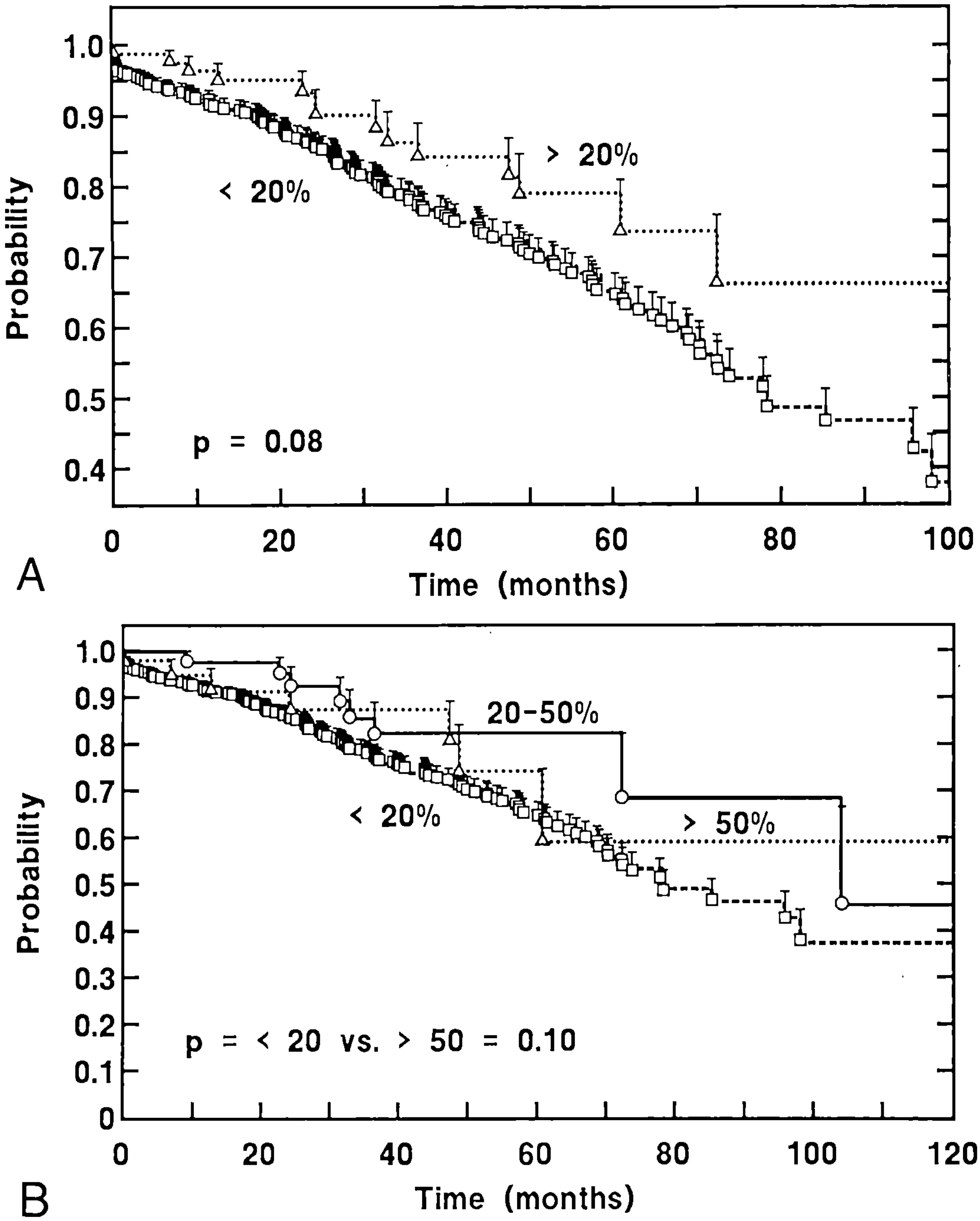
known predilection to restenosis. Patches generally were placed from the distal extent of the internal carotid arteriotomy, distal to the level of intimal endarterectomy, into the proximal level of the common carotid artery. Thirty-one of the eighty patches were placed in female patients (38.8%). Patients with carotid patches were not immune to restenosis and, in fact, the restenosis rate in such patients was somewhat higher than in those with primary closure. In female patients with patch closure, the restenosis rate was 16.1% (5 of 31 cases). Restenosis was documented in 37 of 404 patients with primary closure (9.2%) and in 10 of 80 patients with patch closure (12.5%). Of the 40 patients with polytetrafleuroethylene (PTFE) patches, seven were found to have more than 50% restenosis (17.5%) and three of these went on to occlusion. Similar restenosis rates were seen with the fewer cases in which saphenous vein or Dacron was used as the patch material. Patching also failed to reduce the likelihood of late postoperative stroke when compared with primary carotid closure. In addition the two late strokes seen in the 49 patients with significant carotid restenoses were in patients in whom carotid patch closure had been performed. One of these patients was female, the other male. Diabetes, hypertension, and continued smoking were not significant contributors to the likelihood of restenosis.

Table 1 documents cumulative development of restenosis during the first 24 postoperative months. Most of the restenoses were identified within the first 12 months, including all eight vessels that went on to occlusion and 33 of the 34 that subsequently were reported as more than 50% restenosis. However seven other lesions, including four that were normal at 24 months, progressed to more than 50% restenosis more than than 2 years after surgery.

Some evidence of regression of stenosis was documented in seven patients. Five were patients with initial primary arterial closures and two had PTFE patches placed. Of the seven patients with regression, four were male and three were female, their average age was 66.9 years, and one was diabetic. Six of the seven were smokers. None of these patients sustained a postoperative ipsilateral stroke or died during the course of the study. One patient experienced a single transient ischemic attack.

An additional analysis was performed based on the symptomatic indication for the initial surgery. Of 345 arteries operated on for symptoms, more than 50% restenosis was documented in 31 (9%), compared with 18 of 139 vessels (12.9%, NS) operated on for asymptomatic stenosis. Life table analyses of the subsequent outlook indicated a greater probability of survival ($p = 0.03$), a lower probability of stroke ($p = 0.025$), and a much lower probability of any subsequent neurologic event ($p = 0.0005$) for the asymptomatic cases when compared with the patients operated on for symptoms. There was no statistical difference in the rate of significant restenosis in patients operated on for amaurosis fugax, hemispheric transient ischemic attack, or previous stroke.

We undertook two additional analyses based on the Cox form of the proportional hazards regression model. In the first analysis, we analyzed survival as a function of the covariates age, sex, diabetes, smoking, initial surgery, and restenosis. We treated restenosis as a time-dependent covariate in this analysis. When all variables were included



FIGS. 4A and B. (A) Effect of any degree (more than 20%) of carotid restenosis on the probability of remaining free of any subsequent cerebrovascular event (amaurosis fugax, anterior or posterior transient ischemic attack, stroke, or death). (B) Probability of remaining free of subsequent cerebrovascular events is plotted against degrees of carotid restenosis.

in the model, we found that age, sex, diabetes, smoking, and number of carotid procedures were positive risk factors (that is, the mortality risk increased with age, was higher for male than female patients, was higher among diabetics and smokers, and was higher among patients with bilateral carotid operations), but restenosis was a negative risk factor (that is, the mortality risk was smaller among those with restenosis than those without restenosis, adjusting for time of restenosis). The global chi square statistic for this model was $X^2 = 16.69$ (degree of freedom [df] = 6, p = 0.0105). A more refined stepwise analysis was undertaken to assess the relative strengths of the covariates; it was found that only age and diabetes were statistically significant predictors of death ($X^2 = 14.33$, df −2, p = 0.0008).

A second analysis used the endpoint of time to stroke. Using all six covariates in the model, we found that age, smoking, and diabetes were positive risk factors (that is, the risk of stroke increased with age and was higher among diabetics and smokers), but sex, number of carotid operations, and restenosis were negative risk factors (that is, women were at greater risk of stroke than men, patients

TABLE 1. *Cumulative Development of Significant (>50%) Restenosis*

Carotid Status	Number of Patients					
Occluded	6	7	8	8	8	
>50%	16	26	33	33	34	
20% to 49%	1	1	0	0	0	
<20%	3	3	2	2	1	All 7 patients progressed to >50% after 2 years
Normal	12	5	3	4	4	
No data	11	7	3	2	2	
Time (months after surgery)	3	6	12	18	24	

with bilateral operations were at less risk than patients with unilateral operations, and the risk of stroke was less among those with restenosis than those without restenosis, again adjusting for time of restenosis). The global chi square statistic for this model was $X^2 = 18.50$ (df = 6, p = 0.0051). The stepwise analysis showed that only age and smoking were statistically significant predictors of stroke ($X^2 = 17.52$, df = 2, p = 0.0002).

Discussion

Many previous publications have dealt with the incidence, pathologic condition, and resulting symptoms associated with recurrent carotid stenosis after endarterectomy, but to our knowledge the relative risk of subsequent transient or permanent neurologic symptoms or early death in such patients has not been compared with the fate of patients without recurrent carotid disease. The pathogenesis of the earlier recurrent carotid lesions appears to be associated with abnormal lipid metabolism, excessive smoking, and the female sex.[12,13,16,22,28-30] Platelet-mediated myointimal hyperplasia has been implicated in many of these lesions, although there is some early atherosclerotic development that becomes progressively more prominent as the interval from the initial operation to the time of biopsy lengthens.[28,29,31] Platelet or other direct stimulation of the endothelium with subsequent release of growth factors, and smooth muscle migration and proliferation has been proposed as the major pathogenetic mechanism.[32] However the routine use of postoperative antiplatelet adhesive agents has not eliminated this problem. Other approaches to prevent or treat the problem have included efforts at lipid lowering, abolition of smoking, and the use of routine primary patch grafting, particularly with saphenous vein.[22,24,31,33-36]

One important matter is the distinction between residual and recurrent stenosis. Intraoperative completion studies, whether by angiography or ultrasound, clearly identify some patients with residual stenoses that still can be corrected at the time of the initial procedure. Such methods have been emphasized by many and have been used with benefit by Barnes,[19] Zierler,[10] and our group,[13] with reduction but not elimination of the restenosis problem. Some intraoperative control for technical imperfection is important in all carotid surgery.

Routine patch angioplasty closure has been advocated as a method to prevent recurrent lesions (Table 2), and several reports documented a very low incidence of this problem (0% to 4%) with both PTFE and saphenous vein patches.[33-35,37] However more recent publications document a recurrent stenosis rate of 4% to 11% despite patch closure.[22,23,36-39] Our own rate of 12.5% restenosis with carotid patching may reflect the longer follow-up (mean, 42 months) in our report, as well as our practice of selectively using patches in the most difficult anatomic situations. In addition it is of interest that no strokes have been

TABLE 2. *Effect of Patch Graft Closure on Carotid Restenosis*

Author	Year (Reference)	No. of Cases	Mean Follow-up (Months)	Restenosis (%)	Material
Deriu	1984 (33)	60	6–36	0.0	PTFE
Little	1984 (34)	50	1	0.0	Saphenous vein
Sundt	1986 (35)	89	24	4.0	Saphenous vein
Archie	1986 (37)	100	12	0.0	Saphenous vein
Hans	1987 (36)	66	34	4.5	Saphenous vein
Hertzer	1987 (38)	434	21	4.8	Saphenous vein
Ouriel	1987 (22)	70	17	5.7	Dacron
Eikelboom	1988 (39)	67	12	3.5	Saphenous vein
Mattos	1988 (24)	19	15	10.5	PTFE
Present study		80	42	12.5	Mixed; most PTFE

PTFE, polytetrafleuroethylene.

TABLE 3. *Surgery for Carotid Restenosis*

Author	Year (References)	No.	Death (%)	Stroke (%)
Clagett, WRAMC	1983 (43)	29	0.0	3.4
Das, Cleveland, Cl.	1985 (42)	65	3.1	1.5
Piepgras, Mayo Cl.	1986 (20)	57	0.0	10.4
Bartlett, UCSF	1987 (41)	116	1.7	2.6
Kazmers, U. Wash.	1988 (48)	14	0.0	0.0
Present study	1990	10	0.0	0.0
Total		284	1.4%	3.9

observed in the 37 patients with primary closure and restenosis, while two of the 10 patients with restenosis after patching sustained late ipsilateral strokes ($p = 0.06$). There have been two other reports comparing the late clinical outcome of patients with patch closure and primary suture repair, but neither was prospectively randomized.[38,39] In both patch closure reduced but did not eliminate restenosis.

Our findings of a benign clinical course in patients with carotid restenosis suggest that fears regarding the ominous nature of this process have resulted in more frequent postoperative screening, and perhaps earlier reoperation, in asymptomatic patients with severe restenosis than is justified. Data supporting aggressive reoperation have been presented by Zbornikova,[40] and this approach is also recommended by Piepgras[20] and by Bartlett.[41] However the recent opinions of DeGroote,[21] Mattos,[24] and the present series support a more conservative outlook.

DeGroote reported life table analyses of patients with hemodynamically significant recurrence and a 'reassuringly low' incidence of recurrent symptoms.[21] However the overall likelihood of ipsilateral symptom recurrence was 22% at 7 years, or 3% per year, and the probability of symptom recurrence was stated to be approximately three times higher in the restenotic patients (3% per year) than the normal postoperative group (1% per year). In an independent observation, Mattos et al.[23] found that 'patients with recurrent stenosis remained stable and had infrequent symptoms.' Frequent postoperative duplex studies were thought to be unnecessary and not cost-effective. Our experience tends to confirm the latter approach to the early restenosis phenomenon.

The largest experience in the surgical repair of recurrent carotid lesions (Table 3) has been reported by Piepgras[20] (57 cases), Das[42] (65 cases), and Bartlett[41] (116 cases). In the Piepgras report[20] there were no operative deaths, but four major and two minor strokes (10.4%) represented four times the morbidity rate for primary carotid operations in the same institution (Mayo Clinic). The Cleveland Clinic experience included a mortality rate of 3.1%, and a 1.5% permanent stroke rate.[42] Bartlett's review of the experience in San Francisco[41] documented five strokes (4.3%), resulting in two deaths. Most experienced surgeons agree that reoperations should include a patch closure in almost all instances. Our own smaller experience with reoperative carotid surgery has been free of complications, but the data reviewed in this report have convinced us to be more conservative in recommending surgery to patients with asymptomatic stenoses unless they appear to be threatening to occlude (*e.g.*, more than 90%). In such cases transcranial Doppler evaluation of the intracerebral collaterals may help evaluate the ability of the patient to tolerate possible occlusion of the affected vessel.

Finally consideration of the pathogenetic mechanism most likely to be involved suggests that the risk factors that have been identified, including the female sex, persistent smoking, and hypercholesterolemia, are not known to be involved in platelet-mediated reactions.[29-32,43-46] In addition the common use of postoperative antiplatelet adhesive agents has not eliminated this problem. In sharp distinction to the role of preoperative antiplatelet therapy with aortocoronary saphenous vein grafts,[47] there is no convincing data justifying antiplatelet therapy in recurrent carotid stenosis. Thus, at this time, the etiology and pathogenesis of this healing aberration remain obscure, the implications of the condition are generally benign, and surgical intervention should be limited to those patients who are symptomatic or who have critical stenoses in which progression would be likely to produce significant cerebral ischemia.

The data presented in this report appear convincing that carotid restenosis that remains asymptomatic should be considered a relatively common but benign event. More surprising, however, is the likelihood that such patients are actually 'protected' against future cerebrovascular events. Because this result was not anticipated and not intuitive, considerable effort has been spent in reviewing the data from many different aspects, as well as carefully reviewing the statistical analyses. These efforts have satisfied us that the observations are accurate and the conclusions justified. To explain these findings, we can only speculate that the myointimal covering of the endarterectomized area may inhibit the subsequent development of progressive atheromatous recurrence, degeneration, and embolization. In those patients with early (less than 2 years after operation) restenosis who have come to reoperation, the lesions within the carotid bifurcation are generally described as smooth and nonulcerated. Thus we propose the possibility of competing mechanisms for healing the endarterectomized area—recurrent atherogenesis and myointimal hyperplasia. This explanation seems consistent with the pathologic material presented by Clagett.[45] The factors governing each of these mechanisms remain to be elucidated.

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Alanyl-glutamine Counteracts the Depletion of Free Glutamine and the Postoperative Decline in Protein Synthesis in Skeletal Muscle

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Skeletal muscle protein and amino acid metabolism change after surgical trauma during a period characterized by skeletal muscle protein catabolism. Available total parenteral nutrition (TPN) not containing glutamine does not prevent these changes, while TPN enriched with glutamine has been shown to have beneficial effects on postoperative skeletal muscle protein metabolism. Glutamine, in the form of a dipeptide, alanyl-glutamine, was added to TPN. Patients undergoing elective cholecystectomy were given postoperative TPN. Two groups received isocaloric and isonitrogenous conventional TPN, one group with (n = 8) and the other without an addition of alanyl-glutamine (n = 8). Skeletal muscle protein metabolism was studied in muscle biopsy specimens from which the muscle free amino acid pattern and the concentration and size distribution of ribosomes, serving as a measure of protein synthesis, were determined. In the control group, muscle free glutamine decreased by 38.8% ± 6.6% and the polyribosome concentration per mg of DNA decreased by 21% ± 5.2% after operation. In the group given TPN supplemented with alanyl-glutamine, these two parameters of muscle protein and amino acid metabolism did not change significantly. Compared to the control group, whole-body nitrogen balance was improved after operation by the addition of alanyl-glutamine to TPN ($p < 0.01$). Muscle free glutamine and muscle protein synthesis were preserved after operation and the whole-body nitrogen balance was improved by adding glutamine in the form of alanyl-glutamine to TPN. The dipeptide alanyl-glutamine seems to be a suitable means of providing glutamine in a stable form.

SKELETAL MUSCLE IS a source of substrates that are mobilized in connection with trauma to compensate for the increased gluconeogenesis and protein synthesis in other tissues.[1] Hence skeletal muscle waste regularly accompanies the period following trauma and operation. Despite the administration of conventional total parenteral nutrition (TPN), it has not been possible to counteract post-traumatic muscle protein catabolism, which is characterized by a decrease in muscle protein synthesis and an altered pattern of the free amino acids in skeletal muscle.[2,3] Muscle glutamine, which under normal conditions is a nonessential amino acid, decreases approximately 40% after uncomplicated abdominal surgery.[4] The decrease becomes more pronounced if postoperative complications occur.[5] In critically ill patients, the muscle free glutamine concentration may decrease to 10% to 20% of normal values, a metabolic derangement associated with high mortality rate.[5] After surgery the change in muscle glutamine concentration correlates with the decrease in muscle protein synthesis, as assessed by the polyribosome concentration, and with the cumulated whole-body nitrogen loss.[6] In animal experiments the concentration of glutamine correlates with the rate of protein synthesis in sepsis and during protein starvation.[7,8]

Because glutamine is unstable in aqueous solutions, it is not included in commercially available amino acid solutions. To supply patients with postoperative TPN, including glutamine, the amino acid must be added immediately before administration to guarantee the content of glutamine.[9] Postoperative TPN with an addition of glutamine, ornithine-alpha-ketoglutarate, or alpha-ketoglutarate reduces skeletal muscle protein catabolism. Free glutamine concentration, ribosome analysis as a measure of protein synthesis, and nitrogen balance show less pronounced changes compared to conventional TPN.[9-12] Another means of administering glutamine is a stable dipeptide that undergoes hydrolyzation after infusion.

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In the present study conventional TPN was compared with TPN enriched with alanyl-glutamine. The parenteral nutrition was given to patients undergoing elective cholecystectomy, which was used as a reproducible human model of trauma. The results obtained in skeletal muscle regarding the amino acid pattern, ribosome concentration and size distribution, and nitrogen balance indicated a beneficial effect of the alanyl-glutamine–enriched TPN on the postoperative muscle protein metabolism.

Methods

Patients and Study Design

Patients (n = 16) without metabolic diseases, admitted for elective cholecystectomy, entered the study. They were given postoperative TPN containing either a conventional amino acid solution (n = 8) or an amino acid solution with an addition of alanyl-glutamine (n = 8). The characteristics of the patients and of the operative procedure are shown in Table 1.

After an overnight fast, oxicone scopolamine was given as premedication. Anesthesia was induced using fentanyl, diazepam, penthotal, and pancuronium and was maintained with N_2O/O_2 and intermittent doses of fentanyl and pancuronium. Immediately after the induction of anesthesia before the beginning of surgery, a muscle biopsy specimen was taken from the lateral portion of the vastus lateralis muscle approximately 15 cm above the knee by the percutaneous technique.[13] The muscle samples were weighed three times in 24 seconds on an automatic electrobalance (Cahn 30, Cahn Instruments, Cerato, CA) to allow calculation of the wet weight at time zero. Specimens were taken for analysis of ribosomes and the free amino acids. No glucose-containing solutions were given before the sampling. During operation the patients were given 500 to 1000 mL Rehydrex (Pharmacia Infusion, Uppsala, Sweden). For prophylaxis against thromboembolic complications, 500 mL of dextran 70, 60 g/L (Macrodex med natriumklorid, Pharmacia Infusion) was given. The patients were allowed to drink water after operation but not to ingest any other nutrients apart from the TPN specified below. On the morning of the third postoperative day after an overnight fast, a second muscle biopsy was taken from the vastus lateralis muscle using local anesthesia confined to the skin and muscle fascia only. Subjects on medication or requiring transfusion or postoperative antibiotics were not included in the study.

TABLE 1. *Characteristics of the Patients and of the Operative Procedure (Means ± SEM)*

Characteristic	Control	Alanyl-glutamine
Men/women	4/4	4/4
Age (yrs)	50 ± 4	48 ± 5
Weight (kg)	74 ± 6	74 ± 3
Height (cm)	170 ± 3	173 ± 2
Intraoperative blood loss (mL)	300 ± 60	210 ± 30
Operating time (min)	111 = 18	95 ± 10

TABLE 2. *Nutrients per Kilogram Body Weight per 24 Hours*

Nutrient	Control	Alanyl-glutamine
Energy (kJ)	135	135
Nitrogen (g)	0.2	0.2
Nonessential amino acids (mg)	830	903
Essential amino acids (mg)	645	410
Glutamine (mg)	—	235

The patients were informed about the purpose, procedure, and possible risks involved in the study before their informed consent was obtained. The experimental protocol was approved by the Ethics Committee of the Karolinska Institute, Stockholm, Sweden.

Intravenous Nutrition

After operation patients were given isocaloric (135 kJ/kg bw/24 hr of nonprotein calories) and isonitrogenous (0.2 g N/kg bw/24 hr) TPN for 3 days (Table 2). The nonprotein calories were supplied as isocaloric amounts of glucose (Glukos 20%, Pharmacia Infusion) and fat (Intralipid 20%, KabiVitrum, Stockholm, Sweden). On the day of operation one half of the daily amount of TPN was administered between 3 P.M. and midnight and during the 2 following days TPN was given between 9 A.M. and midnight. Saline was given between midnight and 9 A.M.

The control group (n = 8) received a balanced amino acid solution (Vamin 9, KabiVitrum) and the other group Vamin 9 with an addition of 0.354 g/kg bw/24 hr of alanyl-glutamine (Pfrimmer, Erlangen, FRG). In the latter group, the amount of Vamin 9 was reduced to allow for the nitrogen content of the added dipeptide and still maintain the amino acid supply isonitrogenous compared to the control group.

Amino Acid Analysis

Biopsy specimens of 20 to 30 mg wet weight of muscle, stored for no longer than 3 months at −80 C, were used for amino acid analysis. The samples were homogenized in sulphosalicylic acid and the precipitated proteins were sedimented by centrifugation.[4] The free amino acids in the supernatant were separated and quantified by ion exchange chromatography using an automated amino acid analyzer (Alpha Plus, LKB, Bromma, Sweden) using DC-6 ion exchange resin (Durrum, Interaction, CA) and lithium citrate buffers. The concentrations of the free amino acids in skeletal muscle were determined per kilogram of muscle wet weight.

Ribosome Analysis

Muscle specimens of 60 mg wet weight, stored at −80 C were analyzed within 4 weeks after sampling, as described by Wernerman et al.[14] Briefly, the samples were homogenized in a medium containing a ribonuclease inhibitor. The homogenate was centrifuged for 10 minutes at 1500*g*. The pellet obtained, containing the nuclei, was saved for the determination of DNA by a fluorescence method using salmon DNA as standard.[15] The supernatant was ultracentrifuged for 2 hours at 102,000*g* to separate ribosomes from particles of low molecular weight. The pellet containing the ribosomes was resuspended and layered onto a linear gradient of sucrose between 0.4 mol/L (molar) and 1.5 mol/L. The sucrose density gradient was ultracentrifuged at 149,000*g* for 60 minutes in a swing-out rotor. After centrifugation the gradient was pumped through a continuous-flow cuvette and the absorbance was measured at 260 nm. The area under the curve thus obtained was measured and the peaks corresponding to the 40S and 60S subunits and 80S monoribosome and polyribosomes were identified. The percentage of polyribosomes out of the total quantity of ribosome particles was calculated. The total ribosome concentration was read spectrophotometrically at 260 nm and expressed as optical density units per milligram of DNA. By multiplying the percentage of polyribosomes by the total ribosome concentration, the polyribosome concentration per milligram of DNA was calculated.

Nitrogen Balance

Urine was collected in 24-hour samples and saved for determination of urea, ammonia, and creatinine. The nitrogen balance was calculated, assuming the nonurinary nitrogen losses to be 1.5 g per 24 hours in each individual. The whole-body urea pool was constant because serum urea concentrations did not change significantly in any individual during the study period.

Statistics

All values are given as means ± standard error of the mean (SEM). Student's t test for paired samples was used to compare preoperative and postoperative observations within the groups.[16] The means of the differences between the paired samples of the groups were compared using Student's t test for unpaired samples.

Results

Following cholecystectomy, protein synthesis and amino acid concentrations in skeletal muscle and plasma and the whole-body nitrogen balance were analyzed. The patients received TPN containing amino acid solutions with or without the addition of alanyl-glutamine.

Ribosome Parameters

In the control group receiving conventional TPN, the total ribosome concentration per milligram of DNA decreased after operation by 16% ± 2.8% ($p < 0.001$), and the polyribosome concentration per milligram of DNA decreased by 21% ± 5.2% ($p < 0.01$) (Table 3, Fig, 1). The proportion of polyribosomes relative to total ribosomes remained unchanged. The experimental group receiving TPN supplemented with alanyl-glutamine showed no significant postoperative changes in the total ribosome concentration per milligram of DNA, the polyribosome concentration per milligram of DNA, or the proportion of polyribosomes relative to total ribosomes (Table 3, Fig. 1). Compared to the control group, the concentration of polyribosomes was preserved after operation in the alanyl-glutamine group ($p < 0.05$). Due to difficulties in obtaining adequate amounts of muscle specimens in the alanyl-glutamine group, ribosome analyses were performed in six subjects only.

Muscle Amino Acids

The total concentration of amino acids in skeletal muscle decreased after operation in the control group by 24.7%

TABLE 3. *Total Ribosome Concentration, Percentage of Polyribosomes in the Total Quantity of Ribosomes, and the Polyribosome Concentration Before Operation and on the Third Postoperative Day*

	Control		Alanyl-glutamine	
	Day 0	Day 3	Day 0	Day 3
Total ribosome concentration (OD/mg DNA)	49.8 ± 7.6	41.8 ± 7.4†	49.2 ± 4.8	47.3 ± 4.5‡
Percentage of polyribosomes out of total ribosomes (%)	51.5 ± 2.2	50.2 ± 3.5	50.6 ± 2.7	51.2 ± 2.8
Polyribosome concentration (OD/mg DNA)	24.8 ± 3.0	19.6 ± 2.2*	25.1 ± 3.0	25.2 ± 3.2‡

* $p < 0.01$, † $p < 0.001$ significant difference within the groups compared to the values noted before surgery.

‡ $p < 0.05$ significantly different postoperative change compared to the control group.

The patients received conventional TPN ($n = 8$) or TPN with an addition of alanyl-glutamine ($n = 6$). The values are given as means ± SEM. OD, optical density.

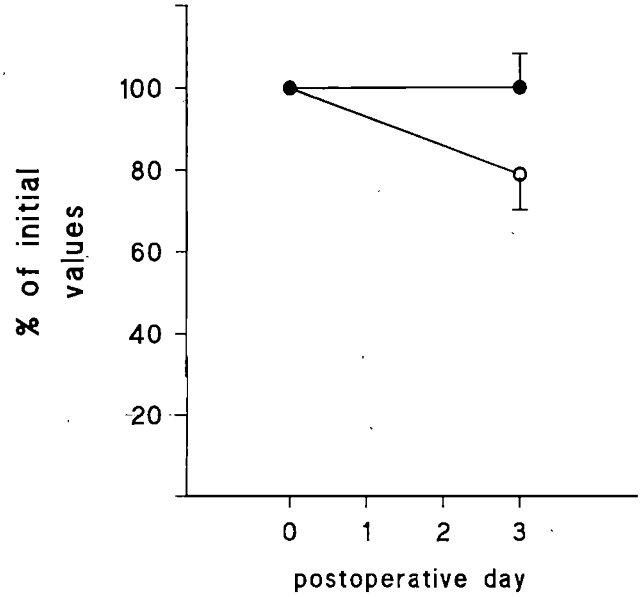

FIG. 1. The polyribosome concentration in skeletal muscle on the third postoperative day in percentages of preoperative values. Patients received either conventional amino acid solutions (n = 8; open circles) or alanyl-glutamine (n = 6; filled circles) as part of postoperative TPN. The otherwise obligatory decrease in the polyribosome concentration was counteracted in the group supplied with the dipeptide, alanyl-glutamine ($p < 0.05$).

± 4.3% compared to the initial level (Table 4). Glutamine decreased by 38.8% ± 6.6%, representing the major portion of the postoperative change ($p < 0.001$; Fig. 2). In contrast the glutamine level was better preserved after operation in the group given alanyl-glutamine compared to the control group ($p < 0.05$). The basic amino acids (lysine, histidine and arginine) decreased after operation by 26.6% ± 6.5% in the control group. These postoperative changes did not occur in the group supplied with alanyl-glutamine (Table 4). The sum total of branchel chain amino acids increased significantly after operation in the control group, but no significant differences occurred in the alanyl-glutamine group. In both groups a postoperative rise was seen in the concentration of phenylalanine, but tyrosine increased only in the alanyl-glutamine group.

Plasma Amino Acids

Differences in the plasma amino acid pattern were noted between the control and alanyl-glutamine–supplemented TPN group. Serine, alanine, and tryptophane increased and glutamate decreased significantly in the control group but not in the alanyl-glutamine group (Table 5). Tyrosine increased and asparagine and glycine decreased significantly in the alanyl-glutamine group but not in the control group. In both groups a significant increase in phenylalanine and aspartate and a decrease in ornithine were noted.

Nitrogen Balance

The whole-body nitrogen balance was negative on every postoperative day in the control group (Table 6), while

TABLE 4. *Concentrations of Amino Acids in Skeletal Muscle (mmol/kg wet weight muscle) Before Operation and on the Third Postoperative Day Following Elective Cholecystectomy*

	Control	
	Day 0	Day 3
Tau	13.65 ± 1.16	12.53 ± 1.25
Asp	0.94 ± 0.13	0.79 ± 0.08
Thr	0.63 ± 0.05	0.76 ± 0.03*
Ser	0.71 ± 0.06	0.85 ± 0.07
Asn	0.26 ± 0.04	0.32 ± 0.04
Glu	3.49 ± 0.37	2.27 ± 0.23†
Gln	13.73 ± 1.13	8.40 ± 0.67‡
Gly	1.26 ± 0.08	1.21 ± 0.09
Ala	2.50 ± 0.32	2.86 ± 0.35
Val	0.29 ± 0.02	0.34 ± 0.01*
Ile	0.07 ± 0.01	0.08 ± 0.02
Leu	0.20 ± 0.02	0.23 ± 0.03
Tyr	0.15 ± 0.04	0.15 ± 0.02
Phe	0.10 ± 0.02	0.14 ± 0.02*
Orn	0.28 ± 0.05	0.18 ± 0.04*
Lys	1.00 ± 0.14	0.71 ± 0.11†
His	0.48 ± 0.09	0.39 ± 0.08
Car	5.86 ± 0.53	5.47 ± 0.58
Arg	0.46 ± 0.10	0.34 ± 0.04
ESSAA	2.45 ± 0.20	2.44 ± 0.12
TOTAA	26.61 ± 1.75	20.05 ± 0.85‡
BCAA	0.55 ± 0.02	0.64 ± 0.03*
Basic AA	1.85 ± 0.33	1.35 ± 0.22†
	Alanyl-glutamine	
	Day 0	Day 3
Tau	14.79 ± 1.25	13.90 ± 1.35
Asp	0.99 ± 0.12	0.87 ± 0.09
Thr	0.88 ± 0.12	0.90 ± 0.10
Ser	0.77 ± 0.04	0.89 ± 0.06
Asn	0.59 ± 0.08	0.53 ± 0.07
Glu	4.05 ± 0.50	3.07 ± 0.30*
Gln	14.35 ± 0.82	13.06 ± 0.75‖
Gly	1.56 ± 0.19	1.37 ± 0.11
Ala	2.80 ± 0.35	3.46 ± 0.39
Val	0.29 ± 0.05	0.33 ± 0.05
Ile	0.15 ± 0.03	0.17 ± 0.02
Leu	0.23 ± 0.03	0.24 ± 0.03
Tyr	0.11 ± 0.01	0.16 ± 0.01†
Phe	0.10 ± 0.01	0.15 ± 0.02*
Orn	0.36 ± 0.03	0.31 ± 0.03
Lys	1.43 ± 0.11	1.44 ± 0.09
His	0.80 ± 0.13	0.77 ± 0.06
Car	4.82 ± 0.89	5.26 ± 0.79
Arg	0.54 ± 0.09	0.46 ± 0.04
ESSAA	3.21 ± 0.25	3.43 ± 0.18
TOTAA	30.04 ± 1.69	28.24 ± 1.41§
BCAA	0.65 ± 0.09	0.74 ± 0.08
Basic AA	2.59 ± 0.28	2.67 ± 0.14§

* $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$ significant difference postoperatively compared to values obtained before surgery within the groups.

§ $p < 0.05$, ‖ $p < 0.01$ significantly different postoperative change compared to the control group.

Patients were given either conventional TPN or TPN with an addition of alanyl-glutamine. Means ± SEM.

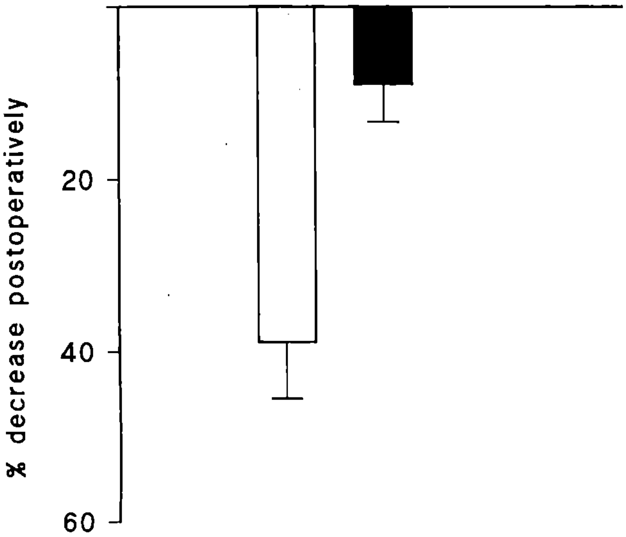

FIG. 2. The postoperative glutamine concentration in skeletal muscle as percentages of initial values in patients undergoing elective cholecystectomy supplied either with postoperative TPN containing a conventional amino acids solution (n = 8; open bar) or one enriched with alanyl-glutamine (n = 8; filled bar). The glutamine concentration was preserved in the alanyl-glutamine group after operation compared with the control group ($p < 0.01$).

nitrogen balance was maintained in the alanyl-glutamine group. The cumulated nitrogen balance was less negative in the alanyl-glutamine group in comparison with the control group ($p < 0.01$; Fig. 3).

Discussion

The first reports that the postoperative depletion of muscle glutamine and the decline in muscle protein synthesis can be attenuated by nutritional means appeared only a few years ago when TPN was supplemented with ornithine-alpha-ketoglutarate.[10] Because alpha-ketoglutarate is the carbon skeleton of glutamine, the obvious suggestion was that provision of glutamine, or an analogue to glutamine, may counteract the protein catabolism seen in skeletal muscle after trauma. This hypothesis has been supported by more and more evidence as a number of investigations have been presented in which glutamine, alpha-ketoglutarate, or the dipeptide alanyl-glutamine were added to postoperative TPN.[9-12,17] All investigations presented so far show beneficial effects on skeletal muscle protein and amino acid metabolism in patients not routinely subjected to postoperative TPN. Although a nitrogen-sparing effect of 10 to 20 g in the immediate postoperative period corresponds to 300 to 500 g of muscle tissue, it is doubtful whether such a finding alone justifies the use of glutamine or glutamine-analogue–containing amino acid solutions in clinical practice.

Glutamine is synthesized in skeletal muscle by amination and transamination reactions. *In vitro* experiments show that isoleucine, valine, asparagine, aspartate, and glutamate are sources for the production of glutamine in skeletal muscle.[18] These amino acids are metabolized through intermediates of the tricarboxylic acid cycle and

TABLE 5. *Concentration of Plasma Amino Acids (μmol/L) Before and on the Third Day Following Elective Cholecystectomy*

	Control	
	Day 0	Day 3
Tau	85.0 ± 12.2	87.2 ± 5.7
Asp	6.2 ± 0.6	7.7 ± 0.8*
Thr	159.3 ± 13.0	192.1 ± 18.7
Ser	141.5 ± 10.2	167.1 ± 17.4*
Asn	68.4 ± 3.5	71.5 ± 7.6
Glu	67.9 ± 8.1	52.3 ± 8.6*
Gln	664.3 ± 24.3	643.6 ± 25.7
Gly	249.0 ± 21.8	248.9 ± 22.2
Ala	344.5 ± 16.2	473.2 ± 38.3*
Val	269.0 ± 16.7	325.1 ± 25.8
Cys	70.9 ± 4.3	66.1 ± 4.4
Met	29.5 ± 2.0	37.8 ± 2.4
Ile	63.9 ± 5.6	73.7 ± 7.0
Leu	146.8 ± 11.1	163.7 ± 17.1
Tyr	65.0 ± 5.3	82.0 ± 7.7
Phe	64.0 ± 5.2	94.5 ± 6.0†
Orn	78.7 ± 9.8	53.9 ± 2.4*
Lys	203.4 ± 13.1	191.1 ± 16.3
His	103.3 ± 6.0	96.7 ± 3.7
Try	45.2 ± 4.1	57.8 ± 6.6*
Arg	94.9 ± 7.0	88.9 ± 7.5
ESSAA	1071.9 ± 61.0	1232.1 ± 78.9
TOTAA	2963.4 ± 106.5	3183.2 ± 124.8
BCAA	479.7 ± 32.7	568.5 ± 47.5
	Alanyl-glutamine	
	Day 0	Day 3
Tau	82.5 ± 8.2	101.8 ± 11.5
Asp	5.5 ± 0.6	8.4 ± 1.7*
Thr	156.0 ± 10.7	169.6 ± 15.1
Ser	142.9 ± 7.9	134.3 ± 4.6‡
Asn	77.7 ± 7.0	59.1 ± 3.6*
Glu	62.4 ± 13.5	58.2 ± 8.5
Gln	802.4 ± 42.4	710.6 ± 26.7
Gly	321.4 ± 44.3	261.9 ± 29.3*
Ala	416.3 ± 48.8	476.5 ± 38.0
Val	295.9 ± 32.2	311.9 ± 20.1
Cys	73.8 ± 6.6	64.9 ± 3.9
Met	28.1 ± 2.5	35.9 ± 2.5
Ile	69.6 ± 8.0	83.8 ± 7.4
Leu	166.3 ± 18.4	172.7 ± 15.9
Tyr	59.6 ± 7.1	75.9 ± 5.5*
Phe	63.8 ± 6.5	91.4 ± 6.7†
Orn	75.4 ± 6.5	56.8 ± 5.0†
Lys	220.6 ± 16.0	190.1 ± 8.8
His	116.4 ± 7.8	99.7 ± 4.5
Try	54.5 ± 4.9	66.8 ± 8.5
Arg	102.3 ± 7.4	83.7 ± 7.0
ESSAA	1114.4 ± 95.6	1196.2 ± 49.8
TOTAA	3289.9 ± 224.3	3202.3 ± 102.7
BCAA	531.9 ± 57.1	568.4 ± 40.9

* $p < 0.05$, † $p < 0.01$ significant difference after operation compared to values obtained before surgery.

‡ $p < 0.05$ significantly different postoperative change between the two groups.

One group of patients (n = 8) received conventional TPN, and another group TPN with an addition of alanyl-glutamine (n = 8). Means ± SEM.

TABLE 6. *Nitrogen Balance in g N/24 Hours during 3 Days Immediately Following Elective Abdominal Surgery*

Day	Control	Alanyl-glutamine
Day 1	−1.5 ± 0.6*	0.5 ± 1.1
Day 2	−4.3 ± 1.7*	−1.0 ± 1.4
Day 3	−5.1 ± 2.1*	−1.3 ± 1.5

* $p < 0.05$, significantly different from zero.
The patients received conventional TPN (n = 8) or TPN with an addition of alanyl-glutamine (n = 8). Values are given as means ± SEM.

thus contribute to the pool of alpha-ketoglutarate, the carbon skeleton from which glutamate and, indirectly, glutamine is synthesized. Furthermore the basic amino acids, histidine and arginine, are metabolized through glutamate and they decrease in parallel with glutamine after trauma.[6,12] Together with alanine, glutamine represents 70% of the amino acid efflux from skeletal muscle in the postabsorptive state.[19,20] In connection with trauma the amino acid efflux from skeletal muscle increases, and hence more glutamine is lost.[21,22] The depression of protein synthesis in skeletal muscle makes more amino acids available for the production of glutamine and alanine because the degradation is unaltered after trauma. Concurrently the activity of glutamine synthetase increases,[23] but still the muscle glutamine level decreases.[3,4] A reduction occurs as early as 12 hours after cholecystectomy[24] and the glutamine content continues to decline during the following days.[9,11,12] The efflux of glutamine obviously exceeds the rate of glutamine production in skeletal muscle and eventually depletes the precursors for glutamine production.[6] In the present study, the addition of alanyl-glutamine to postoperative TPN reduced skeletal muscle protein catabolism in terms of maintenance of the muscle glutamine concentration as well as the polyribosome concentrations and also improved whole-body nitrogen balance.

When groups of patients are compared, it is important that they are be well defined and properly characterized. Here patients undergoing elective cholecystectomy were studied and constituted a useful human trauma model. The groups of patients are homogeneous and the operative trauma elicits reproducible postoperative changes in energy, amino acid, and protein metabolism.[6] When studying patients in the intensive care unit, it is difficult to assemble groups of comparable homogeneity undergoing standardized surgical stress. Furthermore circulatory instability, different degrees of inflammatory response, endotoxemia, and medication make interpretations more difficult unless the groups are matched. Because posttraumatic metabolic changes in skeletal muscle develop continuously over time, it is very important to define the stage of disease and also to start the investigation of each subject at a well-defined point in time if the effects of nutritional treatment are to be elucidated.

Muscle protein synthesis was evaluated by determining the concentration and size distribution of ribosomes.[14] This is the only available technique to assess *in vivo* muscle protein synthesis by repetitive measurements. The results leave room for discussions about the qualitative changes in muscle protein synthesis. Here the polyribosome concentration was preserved after operation in the dipeptide group. This is usually the most sensitive marker of changes in protein synthesis.[25]

In recent studies the amount of glutamine analogues given was chosen to match the daily decrease in muscle free glutamine in skeletal muscle tissue. After intravenous administration of alanyl-glutamine, the dipeptide is hydrolyzed in plasma and elimination in the urine is negligible, which makes it an efficient source of glutamine.[26] The amount of alanyl-glutamine given here corresponded to 0.235 g glutamine/kg bw/24 hr. When 0.190 g glutamine/kg bw/24 hr is given after operation to patients undergoing elective colorectal surgery, similar effects on nitrogen balance and muscle glutamine preservation are seen.[17] Although information about other muscle amino acids and muscle protein synthesis is not provided by that study, it can be concluded that no clear dose-response relationship is seen after elective surgery. Already 0.190

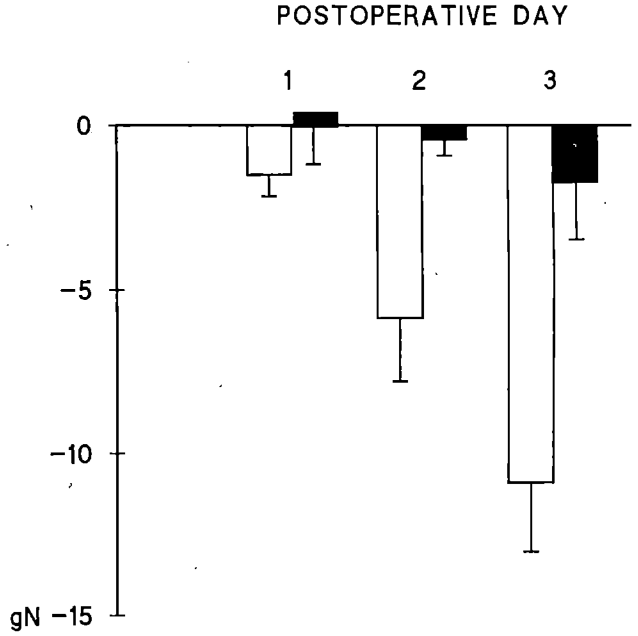

FIG. 3. The cumulated nitrogen balance per day following elective cholecystectomy. Patients were given either conventional TPN (n = 8; open bars) or TPN with an addition of alanyl-glutamine (n = 8; filled bars) after operation. The cumulated nitrogen balance was improved on the third postoperative day in the alanyl-glutamine group compared with the control group ($p < 0.05$).

g glutamine/kg bw/24 hr satisfies the glutamine requirement. This is in accord with findings showing 0.194 g alpha-ketoglutarate/kg bw/24 hr[11] to be as effective as 0.285 g glutamine/kg bw/24 hr.[9] Data available after elective surgery give no indication that provision of glutamine or glutamine-analogues exceeding 0.190 g/kg bw/24 hr are more effective.

Provision of glutamine or glutamine-containing dipeptides lowers or eliminates the efflux of glutamine from peripheral tissues, while the uptake in the splanchnic region remains unaltered.[27] When alpha-ketoglutarate is given, the decrease in free glutamine in muscle is attenuated, but the efflux of glutamine from peripheral tissues is not diminished. This probably reflects the fact that alpha-ketoglutarate is taken up in muscle and facilitates glutamine production.[28] In dogs alpha-ketoglutarate is taken up by most tissues, including skeletal muscle. The kinetics of alpha-ketoglutarate in humans in connection with trauma and sepsis still must be elucidated.

Patients in the intensive care unit have a low content of skeletal muscle glutamine.[5] An extremely low glutamine concentration is associated with a high mortality rate. Patients in this condition also exhibit diminished levels of adenosine triphosphate (ATP) in muscle.[29] It is likely that energy production is impaired. The hypothesis that a low glutamine level is connected with a shortage of tricarboxytic acid cycle intermediates is appealing.[6] Administration of glutamine or glutamine-containing dipeptides to these patients is not likely to raise the glutamine concentration in muscle immediately. Also after elective surgery in otherwise healthy patients muscle glutamine is still not completely restored 30 days after surgery.[30] Provision of glutamine has been shown to diminish the efflux of glutamine from peripheral tissues, but a peripheral uptake has not been demonstrated. Alpha-ketoglutarate, on the other hand, is taken up in peripheral tissues. The biochemical endpoints, when evaluating TPN with an addition of glutamine analogues given to intensive care unit patients, cannot be the same as in patients undergoing elective surgery. In muscle, therefore, diminished ATP levels may be restored fairly quickly, but other alternations will be normalized more slowly if the patients survive. Biochemical endpoints must be sought in the organs consuming glutamine, for example, the intestinal mucosa and immunocompetent cells. There is a paucity of techniques to evaluate *in vivo* metabolism in these tissues. Animal models mimicking the metabolism of intensive care unit patients are not available. Therefore it is a great challenge to develop adequate biochemical parameters to study the possible beneficial effects of glutamine analogues in patients with severely disturbed metabolism. It may be that alpha-ketoglutarate is a suitable support for muscle, which can then supply other organs, while glutamine-containing substances may supply these organs directly, leaving muscle tissue unaffected. A combination of both substances may be the ideal supplement for amino acid solutions in the future.

In conclusion postoperative TPN with an addition of the dipeptide alanyl-glutamine had a beneficial effect on muscle amino acid and protein metabolism as well as on whole-body nitrogen balance. The results are similar to those of recent investigations in which postoperative TPN was supplemented with alpha-ketoglutarate, ornithine-alpha-ketoglutarate or glutamine. Adding alanyl-glutamine seems to be a convenient way to provide glutamine in amino acid solutions. However the most suitable way to prevent glutamine depletion in patients with severe muscle protein catabolism remains to be determined.

Acknowledgments

The authors thank Dr. M. R. Ali, E. Bostedt, C. Hebert, L. Kylander, and L. Thunblad for technical assistance.

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BOOK REVIEWS

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The Southern Surgical Association: The First 100 Years 1887–1987. Robert S. Sparkman (Editor), David C. Sabiston, Jr. and G. Rainey Williams (Assoc. Editors). 533 pp. Philadelphia: JB Lippincott, 1989. $125.00.

THE SOUTHERN SURGICAL ASSOCIATION was originally named the Alabama Surgical and Gynecological Association. However, after its first year, it become the Southern Surgical and Gynecological Association to reflect the true geographical distribution of its members. It was founded in Birmingham by the brothers E. B. Davis and J. D. S. Davis only 20 years after the end of the Civil War, which had devastated the South, destroying its industry and its agricultural systems. Birmingham did not exist at the end of the Civil War, but in the short time thereafter it had become the steel center of the South. The death of the Davis' father, also a physician, in the Battle of Petersburg apparently was a motivating factor in the founding of the Association, in hopes of inspiring the South to regain some of the prestige it had acquired through the achievements of J. Marion Sims of South Carolina and Ephraim McDowell in Kentucky. As the art and science of the practice of surgery became more and more fragmented, the name was shortened in 1960 in deference to those representing all aspects of surgical practice. Even though regional in name, its membership has been national and international since its founding. As early as 1894, five honorary members were elected, one each from France, Germany, Ireland, Belgium, and Italy.

The volume abounds with reports of lasting significance too numerous to cite. Collated by decade, there are interesting and pertinent commentaries on each presidential address, on many of the scientific presentations, along with accounts of the organizational activities and of the contemporary history of the United States and of the world. These are supplemented by the presentations in a symposium at the centennial meeting.

In addition to the scientific aspects, the attendance of the wives of the members and guests has always made the meetings of the Association notable, unique, and enjoyable.

The volume is exceptionally well organized, beautifully printed and bound. The editors, associate editors, consultants, contributors, and the publisher are to be commended highly for their superb accomplishment. I believe the volume will earn and deserve a prominent place in any study of the history of surgery in the era under review.

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Interventional and Surgical Cardiovascular Pathology: Clinical Correlations and Basic Principles. Frederick J. Schoen. 432 pp. Philadelphia: WB Saunders, 1989. $75.00.

THIS GOOD BOOK CONSISTS of 8 chapters, 7 of which were written by Dr. Schoen and 1 of which, the chapter on congenital heart disease, was written by Dr. William D. Edwards from the Mayo Clinic. Some titles of the chapters include General Pathologic Considerations; Ischemic Heart Disease; Valvular Heart Disease; Myocardial, Pericardial, and Endocardial Heart Disease; Assisted Circulation and Mechanical Cardiac Replacement; Disturbances of Rhythm and Conduction; Vascular Disease; and Congenital Heart Disease. Although the chapter on coronary artery disease occupies 50 pages, only 10 of them concern coronary artery bypass grafting operations. The chapter on valvular heart disease has a superb section on mechanical prostheses and bioprostheses. The chapter on congenital heart disease by Dr. Edwards is excellent. It contains much information on baffles and conduits and what they look like after they have been in place for varying periods of time. A valuable feature of this book is the extensive number of references, a total of 3267. The chapter on congenital heart disease alone contains 1209 references. The illustrations throughout the book, for the most part, are of fine quality. If a surgeon were to purchase a 'cardiac pathology book' I believe I would suggest this one, for the moment, as first choice. Furthermore the price seems reasonable in view of the quality of the production.

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Creativity and Disease: How Illness Affects Literature, Art and Music, 5th Edition. Philip Sandblom. 150 pp. Philadelphia: JB Lippincott, 1989. $34.95.

THIS SLIM MONOGRAPH includes carefully selected examples that emphasize the relationship between disease and the creativity of writers, artists, and musicians. The author is a Renaissance gentleman, who happens to be a surgeon, and who in this work manifests his encyclopedic knowledge and love of the arts—literature, painting, and music. The final sentence in the Epilogue expresses the theme of the book,'In great artists, the passion to create generates a willpower strong enough to defeat the worst disease.' Many examples could be selected to illustrate this theme, but two may suffice. Reproductions in color of three of Monet's masterpieces depict the same scene of a bridge as viewed from the garden at Giverny. The first painting is from his youth, the next from when he had developed cataracts, and the last followed the treatment of his cataracts. Each masterpiece is different, particularly in coloration and in sharpness of focus, and reflects the impact of his varying visual acuity on his art. For a devotee of Beethoven, his deafness is awesome to contemplate; he never heard the music. This edition has been revised to reflect advances in medical knowledge in recent years that might alter interpretations of the impact of a specific disease on the creativity of the artist. New examples also are included.

In reflecting on the effect of illness on creativity, I cannot but contemplate the impact of illness on the art as contrasted to the science of surgery. Surgery is indeed an art and the obvious example of the impact of illness on that art would be conjecture on the role of Halsted's struggle for control of drug dependence on the evolution of an entire school of surgery. In his Postscript the author regards the current edition 'for the time being, as the definitive one.' Perhaps Dr. Sandblom might consider the impact of disease among surgeons on their creativity and provide us, in a few years, with another edition of his unique monograph.

Society is indeed indebted to Dr. Sandblom for focusing on these relationships. The interested reader, physician or nonphysician, will be enriched by perusal of this volume. Dr. David C. Sabiston, Jr. in a review of a previous edition (Annals of Surgery 1982; 198:108) stated 'The Profession is deeply indebted to this great scholar whose knowledge, contributions and influence across many fields have been immeasurable.'

ARTHUR J. DONOVAN, M.D.
Los Angeles, California

Atlas of Cardiothoracic Surgery. L. Henry Edmunds Jr., William I. Norwood, and David W. Low. 287 pp. Philadelphia: Lea & Febiger, 1990. $125.00.

THIS BOOK IS A comprehensive atlas of cardiothoracic surgical procedures. The breadth of this atlas sets it apart from most contemporary atlases of cardiac or thoracic surgery. Excluding endoscopy, all areas of adult and pediatric cardiac surgery, as well as pulmonary, chest wall, and esophageal surgery are covered. This compact volume is very well organized and clearly presents all the essential steps for each procedure.

This atlas is divided into six sections: (1) basic incisions, (2) acquired heart diseases, (3) aorta, (4) congenital cardiothoracic surgery, (5) pulmonary and mediastinal operations, and (6) esophageal disease. The text is concise and clearly linked with the facing numbered pen and ink illustrations. The drawings are above average and consistently from the surgeon's viewpoint. The wide variety of operative approaches presented reflects the broad experience of the authors. The techniques that are illustrated and described are both current and widely accepted as preferred. As a concise atlas, no effort is made to include physiology, but nuances of technique are included frequently. The index is quite complete.

There are very few weaknesses in this volume. Retrograde cardioplegia and repair of aortic dissections are not specifically discussed. Both apical-aortic conduit placement and the Konno procedure are illustrated fully twice, once in the adult aortic stenosis section and once in the congenital section.

The infrequent flaws are far outweighed by the authoritative, crisp textual descriptions and the clarity of the illustrations. No competing atlas covers all areas of thoracic surgery in one reasonably sized volume. I recommend this book to anyone wanting a single atlas encompassing the majority of cardiothoracic surgery. This volume will be particularly popular with general and thoracic surgery residents because its quality and breadth are unmatched in its relatively reasonable price range. For the surgeon in practice, this book will provide a wide-ranging technique refresher, but not the details of why or when to use various techniques. This book should become the standard basic cardiothoracic surgery atlas in medical libraries.

JON F. MORAN, M.D.
Kansas City, Kansas

Invasive Cardiology: Principles and Techniques. Thomas M. Bashore. 318 pp. Philadelphia: BC Decker, 1990. $62.50.

DURING THE PAST 10 YEARS, the development of percutaneous transluminal coronary angioplasty (PTCA) and multiple forms of thrombolytic therapy have been at the forefront of a virtual explosion in interventional cardiology. Most of these therapies have resulted from advances that occurred in radiologic and biomedical technology. During this time the cardiac catheterization suite has changed from a diagnostic center to a laboratory where both diagnosis and therapy are effected.

This timely book by Dr. Bashore and his colleagues is addressed to both physicians and nonphysicians in its description of a modern interventional cardiac catheterization laboratory. The 14 chapters in the text are authored by physicians and technologists, and each one deals with a different aspect of the laboratory. The text begins with an overview of a modern cardiac catheterization suite. A thorough presentation of modern angiographic imaging systems follows, along with a comprehensive discussion of modern angiographic data acquisition techniques and data analysis. The current indications for cardiac catheterization are discussed by Dr. Bashore, who is director of the cardiovascular laboratory at Duke University Medical Center and editor of this text. A complete discussion of the complications that result from cardiac catheterization procedures as well as their treatment follows. There is an excellent chapter on the basic anatomy and physiology of the heart, along with a discussion of the common disease states that often require cardiac catheterization for diagnosis and therapy. A chapter on pharmacology addresses not only the drugs that are used to directly affect the cardiovascular system but also contains a description of the types of sedative and anxiety-reducing agents used to make patients comfortable during interventional procedures. The final chapter describes those catheter techniques that are used to perform invasive electrophysiology studies in patients who have a variety of complex supraventricular and ventricular arrhythmias.

The text is replete with multiple illustrations, including pictures of the common types of equipment that are used in a modern cardiac catheterization laboratory as well as hemodynamic and angiographic examples of the types of data that can be obtained during these studies. By design, the references at the end of each chapter include basic articles and review articles of appropriate subject matter.

This text is recommended reading for the entire cross-section of health professionals who are involved with interventional cardiology. Dr. Bashore and his colleagues are to be commended for this excellent addition to the cardiovascular literature.

T. BRUCE FERGUSON, JR., M.D.
St. Louis, Missouri

Care of the Surgical Patient (Vol. 1—Critical Care; Vol. 2—Elective Care). Douglas W. Wilmore, Murray F. Brennan, Alden H. Harken, James W. Holcroft, and Jonathan L. Meakins. 1500 pp. New York: Scientific American Medicine, 1989. $225.00.

THIS TWO-VOLUME TEXT, edited by five knowledgeable leaders in the field of management of surgical patients, is a largely successful attempt to provide readers with a comprehensive discussion of the management of surgical patients that is also easy to read. It concentrates primarily on perioperative management and combines basic science and physiology with useful practical information. Volume one covers critical care, trauma, and burns. Volume two is concerned with care of the elective patient and has sections on pediatrics, special problems in perioperative care, and the diagnosis and management of surgical infections. Each chapter begins with an algorithm that is used as a framework for subsequent in-depth discussion of the subject matter. Some of the algorithms are rather complicated and difficult to follow, but for the most part they are well done and concise.

The authors of individual chapters have been carefully chosen for their expertise and present the information in a well-organized and easily understood manner. One of the unique features of the book is that it is loose-leaf and frequently updated with mailed inserts designed to replace parts of the individual chapters as they are improved and new information is added. The updates that have been provided so far have been well done and have improved an already excellent text.

The volumes are published by Scientific American and the influence of the publisher in the organization of the book is apparent. The diagrams and illustrations are outstanding.

Care of the Surgical Patient is a much needed comprehensive overview of surgical care. It is generally well written and is illustrated magnificently. The sections on critical care and trauma are particularly well done and are important new contributions to the surgical literature. Frequent updates allow for continuous improvement of the book and ensure that the chapters remain relevant and current. *Care of the Surgical Patient* is a highly recommended reference useful on a daily basis for those involved in the management of surgical patients.

DAVID H. WISNER, M.D.
Sacramento, California

Smith's Anesthesia for Infants and Children, 5th Edition. Etsuro K. Motoyama, Ed. and Peter J. Davis, Assoc. Ed. 948 pp. St. Louis: CV Mosby, 1990. $89.00.

THE EXPANDING DIMENSIONS and the explosion of knowledge in the field of pediatric anesthesia are reflected in the size and contents of the fifth edition of this book. The new editors are to be complimented; they have succeeded in producing a valuable textbook, although the benefits of drawing on North American sources only for all 30 of the contributors (more than one third of whom are from the Children's Hospital of Pittsburgh) are debatable.

The book's 33 chapters and 948 pages are divided into four parts (Basic Principles, General Approach, Clinical Management of Special Surgical Problems, and Associated Problems in Pediatric Anesthesia) and there are five useful appendices and a very good index. The text reads easily and the style is remarkably uniform throughout. Discussion is mostly very adequate and each chapter has extensive and up-to-date references. Repetition is minimal and indeed is wisely not avoided because it adds to the continuity of the text. I did not set out to read the whole book, but became absorbed in the contents and found myself doing so.

Subject matter that is not available in other recent textbooks deals with Organ Transplantation, Safety, and the Medicolegal Aspects of Pediatric Anesthesia. The latter, coauthored by Robert Smith, the editor of the first four editions of this book, abounds with wisdom born of years of experience and is one that should be read by everyone who practices the art and science of the subspeciality. For those interested in the history of Pediatric Anesthesia, a few pages on the subject would have been appreciated. I liked the approach adopted in the chapter on intensive care wherein the authors thoroughly address only those 'principles of pediatric critical care that apply specifically to the practice of anesthesia,' referring the reader who seeks more information to the excellent dedicated textbooks available.

Should you buy this book? It will add to the knowledge and wisdom of anyone who reads it, regardless of seniority. It is certainly good value for money and should be in every institutional and personal library, even if you only treat the occasional pediatric patient.

EDMOND C. BLOCH, M.D.
Durham, North Carolina

LETTERS TO THE EDITOR

January 9, 1990

Dear Editor:

Clavien and colleagues are to be congratulated on their excellent paper 'Acute pancreatitis and normoamylaseamia' (Ann Surg 1989; 210:614–20). We concur entirely that computerized tomography (CT) scanning should be used in cases of doubtful or negative enzymatic results. They state that 19% incidence of normoamylaseamia found in their series is '... significantly higher than commonly admitted,' and that '... future classifications of pancreatitis [should] mention the fact hyperamylaseamia is not a necessary condition for the diagnosis of AP [acute pancreatitis].'

We see some difficulties, however, in extrapolating their data into a general context. The results of different series will be flavored by referral patterns and the prevalence of different etiologies. To illustrate we examined serial amylase levels in 339 patients with AP (259 with mainly gallstone etiology and 82 with an alcoholic cause), 99% of whom were admitted within 24 hours of the attack and mostly included in other studies.[1–4] Amylase was measured by the Phadebas method, our diagnostic level for AP being more than 1000 IU/L (normal range, 70 to 300 IU/L). On admission hyperamylasemia was present in 99.1% (diagnostic level reached in 94.4%); at 24 hours this was 96.7% (71.7%); at 48 hours it was 72.3% (35.1%); at 72 hours it was 47.6% (7.2%); and at 1 week it was 25.1% (8.2%). Thus it is apparent that the greater the delay in patient admission after the onset of the attack, the greater the likelihood of a normal amylase. Thus the unusually high incidence of normoamylaseamia in the authors' results is partly explained by a considerable delay in the admission of most of their patients.

Even with this proviso, the finding that 58% of 132 alcoholic patients had a normal amylase level seems remarkably high. In our experience 98.8% of alcoholic patients had an amylase level of more than 300 IU/L and this was more than 1000 IU/L in 84.1%.

Perhaps Clavien and colleagues have included in their analysis a proportion of patients with exacerbations of chronic pancreatitis rather than acute pancreatitis *per se.* Clinical judgment and CT scanning are not, in themselves, always sufficient to exclude chronic pancreatitis, as the authors imply. It would have been helpful to know more about the actual outcome of these patients during hospital admission and their subsequent investigation, including endoscopic retrograde cholangiopancreatography. It is difficult to appreciate how it is possible to differentiate by CT alone between acute and chronic pancreatitis in a patient with a normal serum amylase level and who, on CT scanning, has no more than a moderately enlarged pancreas. Certainly in these patients we would endorse the wider use of serum lipase determinations.

The authors state that 'the CT scan appears to be the gold standard in AP'; surely histopathology is the gold standard. This seems to be borne out by the statement that CT in their hands has a sensitivity rate of 92%, which is similar to our own figure of 94%.[2]

Internationally accepted strict criteria for the diagnosis of acute pancreatitis need to be adhered to for comparison of results between different centers and for the undertaking of prospective randomized trials. At a time when general improvements in supportive care and more precise methods of intervention clearly have resulted in improved outcome, it will be difficult to show new advances if series of acute pancreatitis are diluted by cases with chronic pancreatitis alone (enlarged pancreas and normal amylase level), or patients with gallstone disease alone (raised amylase and normal pancreas). It is noteworthy that Clavien and colleagues have presented a large series of patients in whom a diagnostic level of amylase, other than a level above the upper limit of normal, is not even discussed.

While agreeing with their general conclusions, two points must be emphasized. First that where elevated enzyme levels are used without confirmatory CT or histologic examination these should be set at several standard deviations above the normal and include a time definition. Second where CT scanning is used as the main diagnostic investigation in alcohol-related disease, additional criteria are required to exclude chronic pancreatitis or alternatively to confirm an acute attack superimposed on a chronic condition. In the latter case, CT criteria alone may be applicable in some but not all cases. We would entirely endorse the inference of Clavien and colleagues that an improved classification of acute pancreatitis is warranted given the recent advances in diagnostic CT.

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J. P. NEOPTOLEMOS
N. J. M. LONDON
Birmingham, United Kingdom

March 5, 1990

Dear Editor:

We are grateful for the interest shown by Drs. Neoptolemos and London in our recent prospective study on acute pancreatitis (AP). They doubt the general nature of our observation that a significant proportion of patients with AP have normal amylase values on admission to hospital. They based their objections on the level of amylase selected as the cut-off point for normality in our study, on their suggestion that some of our patients may have had chronic pancreatitis, and on the results of their own studies.[1,2]

The purpose of our study was to define the incidence of normoamylasemia on admission in patients with suspected AP by the systematic use of contrast-enhanced CT scan, regardless of amylase values. All patients with serum amylase levels less than 160 IU/L were considered to be normoamylasemic because this value is 3SD above the mean and, by definition, includes 99% of normal individuals. Keeping the purpose of the study in mind, is the choice of an amylase level that is the upper limit of normal really questionable? Neoptolemos and London suggest that a higher level of amylase should have been regarded as the cut-off in our study. If so the percentage of patients with 'normal' amylase levels would have been even greater, and the resulting sensitivity worse.

Turning to their contention that our results might be explained by the inclusion of patients with chronic pancreatitis, we believe there is abundant evidence in our paper that this is not so. All of the patients had suspected AP on clinical grounds. None of the patients had pancreatic calcifications or pancreatic duct dilatation on CT scan, or evidence of exocrine insufficiency. A large proportion (68%) of the normoamylasemic patients had elevated serum lipase, a strong argument in favor of the diagnosis of AP.[3] Furthermore, in Figure 1 of our paper, there were data available showing that even in more severe forms of AP (*i.e.*, CT groups II and III, phlegmon extending in at least one extrapancreatic area), normoamylasemia was present in 14% of the cases on admission. On the other hand, by excluding all patients with previously documented bouts of pancreatitis and similar painful episodes, the incidence of normoamylasemia is still 15.6%. Regarding their remark that studies on AP will be diluted by patients with chronic pancreatitis, if CT standards are adopted, they do not seem to have considered that the omission of normoamylasemic patients may be much more damaging to validity of those studies. Incidently we did not state that '58% of 132 alcoholic patients had normal amylase,' but that of all normoamylasemic patients 58% had evidence of alcohol abuse. Our interpretation of the term 'gold standard' means the best available standard; in Geneva, at least, histology of the pancreas in AP is rarely available.[4]

Next, examining their objections based on their own work, it is critical to note that they define AP in terms of elevated serum amylase level, *i.e.*, 'serum amylase level of greater than 1000 IU/L in the presence of a compatible clinical picture.'[1,2] Of course almost 100% of their AP patients have serum amylase levels greater than 300 IU/L. In fact, given their definition of AP, it is surprising that all patients do not have elevated amylase. Although most authors include hyperamylasemia in their diagnostic criteria of AP, to our knowledge none has used the data to identify the rate of normoamylasemic pancreatitis.[3] Neoptolemos and London take us to task for 'considerable delay in the admission of most patients,' while stating that 99% of their patients were admitted within 24 hours of the onset of an attack. But by defining AP in terms of serum amylase, one might miss the diagnosis in patients arriving later with normoamylasemic AP. By their own figures, almost 30% of patients at 48 hours were normoamylasemic. Have they considered that some patients might arrive at their hospital only when they reach this stage of the disease and, as a result, are not identified as having AP? Their comments about whether our results reflect the 'general context' are conjectural. We will only know about the pertinence and general applicability of the Geneva experience when other centers have examined nomoamylasemia in acute pancreatitis using the approach presented in our study. The percentage of AP patients with normoamylasemia in the area of England studied by Neoptolemos and London may indeed be less than the 19% in the Geneva study, but until they do the study they cannot know the figure. We believe they might be surprised.

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P.-A. CLAVIEN, M.D.
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A. ROHNER, M.D.
Geneva, Switzerland

April 30, 1990

Dear Editor:

We have read with great interest the paper of Drs. Dubois and colleagues, 'Coelioscopic Cholecystectomy,' in the January 1990 issue.[1] The same authors reported, at a later stage, 200 laparoscopic cholecystectomies (LC) of 19 patients were converted at the same session to open surgery. In 16 cases this was due to adhesions or technical difficulties and in three cases because of bleeding. In two patients a 'chole-peritoneum' or bile collection developed, probably due to leakage requiring drainage.[2] Dubois and colleagues should be commended for their contribution.

This intriguing technique has created more controversy and excitement in the surgical community than the publication of Langenbuch's first cholecystectomy[3] or Sauerbruch et al.'s extracorporeal gall stone lithotripsy.[4] In the United States, Reddick and Olsen[5] published their first results. In our institution five surgeons, including us, are performing LC.

We are extremely concerned about patient safety because iatrogenic injuries may occur with this procedure. Clearly competence in diagnostic laparoscopy is a prerequisite to learning how to perform LC. Courses to teach LC are mushrooming and are booked months ahead. Some of these lack a proper curriculum or experienced teachers and many provide limited hands-on experience. Laparoscopic cholecystectomy is one of the most complex endoscopic procedures and needs a great degree of skill to perform it safely and well.

We train residents under supervision for 3 years to do open cholecystectomies before they may sit for their Board examinations. Although LCs do not require years of training, poorly structured crash courses lacking proper endorsement from specific surgical societies or authorities can be extremely harmful.

In addition, there are no guidelines to hospital credentialing or privileging committees and consequently many surgeons without adequate training are performing this procedure. What is more disturbing is that physicians in other disciplines, including gynecology, are performing LCs with or without surgical assistance. There is an urgent need for surgical authorities to issue guidelines to surgeons and hospitals. Biliary surgery was established more than 100 years ago and has a very good reputation and an excellent safety record if operations are performed by well-trained surgeons. Any new procedure, however ingenious, that looks simple in certain hands can look different when performed by others.

There are many misconceptions already on the horizon. For instance a few eager surgeons performing LC have tried to combine a surgical and a nonsurgical treatment of patients younger than 60 years with cholelithiasis and choledocholithiasis. These patients first undergo LC followed by endoscopic sphincterotomy. However this approach can result in complications. In 10% to 15% of patients the common bile duct cannot be cannulated. Sphincterotomy carries a 0.5% to 1% mortality rate, 8% to 10% morbidity rate, and a few days hospitalization. Patients younger than 60 years can be cured in one session by open surgery with no chance of death and only one hospitalization episode.

Other laparoscopic surgeons are already recommending that LCs in subacute or even acute cases can be performed after minimal physician experience. These misconceptions have the potential to cause complications. Larparscopic cholecystectomy is an important milestone in biliary surgery and an adjunct for the treatment of gall bladder disease in a selected group of elective cases performed by competent surgeons. The loopholes of endoscopic training and the assessment of competence must be closed.

We applaud this new procedure because the correctly selected patient and society as a whole gains distinct advantage over open surgery, but we would like to sound our warning to our over-enthusiastic colleagues. We ask the surgical authorities to establish controlled conditions to avoid the disacreditation of a good endoscopic procedure and increase the safety margin for the patient.

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Addendum

Since this letter was submitted, the Society of American Gastrointestinal Surgeons published guidelines for privledging, standards of practice, and training.

GEORGE BERCI, M.D., F.A.C.S.
JONATHAN SACKIER, M.D., F.R.C.S.
Los Angeles, California

April 5, 1990

Dear Editor:

I appreciate the interest of Dr. Berci in my publication on coelioscopic cholecystectomy (CC) and I am very pleased to hear that the technique is 'mushrooming.'

Like Dr. Berci I am concerned about the safety of the patient and the potential risks if CC is performed by inexperienced operators. The same criticism was made when I described, in 1982, the cholecystectomy by minilaparotomy: in the United States, as in Europe, there is no possibility of preventing the unskilled operator from performing a CC as well as any other surgical procedure for which he is untrained.

Nevertheless there are two problems: the training of operators and the limits of CC. The training in laparoscopy is necessary but easy to obtain with models and in watching video endoscopies. I disagree with Dr. Berci on that point and I don't think that competence in diagnostic laparoscopy is a prerequisite, but as long as one can diagnose operative difficulties, such as biliary abnormalities or sudden bleeding, it is imperative that CC should be performed by a surgeon who is qualified in biliary surgery. Two difficulties remain for the few next years: the lack of enough centers for training in laparoscopic surgery and ultimately, if endoscopic surgery increases, the lack of surgeons qualified in open biliary surgery.

It is not easy to foresee the limits of CC. It is evident that a trainee must begin with the uncomplicated cases, but I am not of the same opinion as Dr. Berci about acute cases, which in our practice, are mostly treated by CC (32 acute cases among more than 400 CCs).

It is similar for choledocholithiasis: open surgery is a safe procedure, but CC in association with endoscopic transcystic exploration of the main duct or pre- or postoperative endoscopic sphincterotomy are equally safe if performed by skilled operators.

I fully agree with Dr. Miller's and Dr. Berci's warnings, but I am confident in the responsibility of surgeons and the fine future of endoscopic surgery.

F. DUBOIS
Paris, France

February 27, 1990

Dear Editor:

I found the article 'Anorectal Carcinoid Tumors: Is Aggressive Surgery Warranted?' by Sauven and colleagues (Ann Surg 1990, 211:67–71) very interesting and informative. There is one piece of data, however, that deserves more elucidation.

The authors have presented the largest collection of hindgut carcinoids to date. The heretofore unappreciated association between rectal carcinoids and ulcerative colitis shed further light on the area of carcinoids and associated disease. Of equal interest, however, were the eight patients with concurrent malignancy noted in the review. Although there is a well-recognized (30% to 40%) incidence of synchronous or metachromous tumors associated with carcinoids of midgut origin, the large number of associated malignancies (18%) in this review previously has not been noted with hindgut carcinoids.[1–3] For that reason further information regarding location and types of tumors associated with these hindgut carcinoids would be of great interest.

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THOMAS C. SULLIVAN, M.D., F.A.C.S.
Chicago, Illinois

May 6, 1990

Dear Editor:

We appreciate Dr. Thomas Sullivan's observations regarding our article on anorectal carcinoid tumors.[1] He is concerned with a substantial incidence of synchronous and metachronous neoplasms in this Memorial Sloan-Kettering Cancer Center (MSKCC) series because associated malignancies have not been noted with hindgut carcinoids.[2,3] This increased incidence in our series should be interpreted with caution.

Essentially all patients at the MSKCC have active or treated cancers. All are evaluated thoroughly during the management of their disease. All carcinoid tumors in the eight patients with an associated cancer were discovered during the initial evaluation or follow-up for the 'other' tumor. One of these patients, with symptoms referable to the carcinoid tumor, died of that disease. No patient in the entire series developed a second cancer after identification and treatment of the carcinoid tumor.

Associated tumors included colorectal cancer (3), laryngeal cancer (1), prostate cancer (1), vulvar cancer (1), ovarian cancer (1), breast cancer (1), carcinoid tumor of the appendix (1), and a meningioma (1). One patient had colon, breast, and ovarian cancers. She is alive without disease.

We believe that the high frequency of associated malignancies in this series reflects the hospital's patient population, rather than the biology of hindgut carcinoid tumors.

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E. R. SIGURDSON, M.D., Ph.D., F.R.C.S(C)
J. A. RIDGE, M.D., Ph.D.
S. H. QUAN, M.D., F.A.C.S.
New York, New York

March 8, 1990

Dear Editor:

I read with great interest the article by Green and colleagues (Ann Surg 1990; 211:50–54), especially because the authors's conclusions concerning the risks of incidental cholecystectomy were contrary to those of a number of previous studies. However I believe several aspects of their study deserve further comment. While the authors avoided the disadvantages of using an historical (or other inappropriate) control group, the comparability of their two groups must remain open to question. Operations on the reproductive tract (which were associated with one of the lowest incidence of wound infection) accounted for 32% of control group procedures, but only 6% of the procedures in the cholecystectomized group. Upper gastrointestinal (GI) procedures (which had the highest incidence of wound infection) comprised 10% of control procedures, but 25% of the other groups's procedures. Indeed three of the six wound infections occurred in patients undergoing upper GI surgery. Rather than relying on the calculated adjusted relative risk, these results might suggest that incidental cholecystectomy could increase morbidity when combined with certain primary operations, but not with others. No wound infections occurred in the single largest group of patients among those who had cholecystectomy, *i.e.*, those who had lower GI surgery.

Certainly this paper reopens the debate concerning the safety of incidental cholecystectomy, and further studies are needed, as the authors have suggested. Indeed it is the risk of incidental cholecystectomy relative to that of future morbidity from untreated gallstones that is important. I suspect that we are further than we think from a precise answer to this question.

EUGENE J. GIBNEY, F.R.C.S.I.
Dublin, Ireland

May 31, 1990

Dear Editor:

We thank Dr. Gibney for his thoughtful comments on our paper on the increased rate of morbidity following incidental cholecystectomy.[1] In that analysis we found the rate of postoperative wound infection to be 3.3 times higher and that of other postoperative complications to be 1.7 times higher in surgical patients undergoing cholecystectomy incidental to another surgical procedure than in patients undergoing the same primary surgical procedure without incidental cholecystectomy. This increased risk was independent of several factors that also significantly increased the risk of postoperative infection or other complications, specifically age, diagnosis of malignancy, and category of primary surgical procedure. These factors previously were shown to be associated with an increased risk of postoperative wound infection.[2–4] The increased risk of incidental cholecystectomy, above and beyond these other risk factors, was determined in the statistical analysis controlling for these other factors.

In our study the primary surgical procedure type also significantly affected the risk of complications. Dr. Gibney is correct in observing that the risk of complications was higher with cholecystectomy incidental to some procedures (upper gastrointestinal [GI] tract, solid abdominal organs) than others (retroperitoneal, reproductive tract). Procedures involving the lower GI tract with incidental cholecystectomy had a lower risk of postoperative wound infection but a higher risk of other complications. The fact that no complications were seen with cholecystectomy accompanying primary reproductive tract procedures may indicate that this combination of procedures is rare (with three incidental cholecystectomies per 1000 procedures) or may indicate a truly diminished risk of performing incidental cholecystectomy with this type of procedure.

Our results are consistent with at least one previous, well-conducted study of the risks of incidental cholecystectomy. Kovalcik et al.[5] found increased risks 2.4 times higher for postoperative wound infection and 1.6 times higher for other complications following incidental cholecystectomy, which corresponded remarkably with our findings of 3.3- and 1.7-fold increased risk, respectively. We believe that these findings should reopen the debate about when and where incidental cholecystectomy is safe and advisable. We agree that the ultimate question of the competing risks of removing the gallbladder now *versus* future morbidity from gallbladder disease remains to be resolved.

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September 25, 1989

Dear Editor:

The report by Gouge, Depan, and Spencer in the May 1989 issue of *Annals of Surgery*[1] demonstrates again the difficulties encountered in the treatment of patients who develop sepsis after esophageal perforation. A group of 4 of their 18 patients developed mediastinitis. Two patients in this group were treated with diversion, as recommended by Urschel; one patient underwent resection and one patient was treated with T-tube diversion. Only this last patient survived. The mortality rate for the total series of 18 patients was 17%, yet a mortality rate of 75% was seen for those 4 patients with mediastinitis. However the authors recognize that 'the advanced pathologic condition of the three patients who died was quite different from that of the 14 patients treated by repair with an autogenous pleural flap buttress.'

It is for this subgroup of very sick patients that a different treatment option was proposed by us and reported in January 1986.[2] The emphasis of such treatment is directed to the aggressive treatment of mediastinitis, which is the condition responsible for death in patients with esophageal rupture. Our efforts concentrate on the treatment of the mediastinitis, temporarily accepting the presence of the esophageal opening and taking advantage of it to provide extensive irrigation of the mediastinum through a catheter positioned inside the lumen of the esophagus proximal to the esophageal tear. This irrigation removes from the mediastinum enzymes, bacteria, food particles, and chemical substances responsible for the lethal course of mediastinitis. A chest tube in the mediastinum suctions the irrigant continuously. This technique is described in our January 1986[2] paper. A slightly modified irrigation technique was used for patients with mediastinitis produced by piriform sinus rupture, also with good results.[3] Transesophageal irrigation in the treatment of mediastinitis produced by esophageal rupture is a valuable option for those desperately ill patients.

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May 18, 1990

Dear Editor:

All of our 18 patients had significant mediastinitis. In 14 patients, direct operation for control of the perforation and mediastinitis using suture repair and parietal pleural flap buttress was successful in controlling the mediastinitis and repairing the esophagus, whether carried out shortly after injury or as long as 8 days later. Respiratory, anti-microbial, and nutritional therapy were used as required.

The conditions of the four other patients were judged inappropriate for the Grillo procedure. Two were managed initially at other institutions with tube thoracostomy, which stabilized but did not control the mediastinitis. They were transferred and operated on 14 days after perforation. One patient had a perforation extending from thoracic inlet to cardioesophageal junction. After treatment by exclusion and diversion, she died of sepsis and mediastinitis uncontrolled by tube thoracostomy, as did the other patient treated by exclusion and diversion. The Abbott T-tube drainage used in the other patient was successful, but morbidity and mediastinitis were prolonged. The last patient had stricture of the distal esophagus disrupted by balloon dilation. Although resection without anastomosis controlled the mediastinitis and allowed subsequent reconstruction, she died of sepsis.

Thus of 16 patients with direct control of the perforation, 15 survived and none died of mediastinitis. Both patients whose perforations and mediastinitis were not controlled directly died.

Dr. Santos and Dr. Frater demonstrated in their 1986 publication[1] that transesophageal mediastinal lavage can be a significant adjunct to the treatment of advanced mediastinitis when direct control of the esophageal leakage is unsuccessful, inappropriate, or impossible.

In our experience primary repair of the esophageal perforation buttressed by a parietal pleural flap has the best chance of controlling sepsis and simultaneously restoring functional continuity of the esophagus. We have now performed the Grillo procedure 17 times, with two temporary fistulas and no deaths.

The limits of esophageal repair with a viable tissue buttress have not been defined yet. When the nature of the esophageal pathologic condition, the patient's condition, or failure of the primary repair procedure leads to continued mediastinitis and sepsis, the mortality rate will be high. In this setting procedures to minimized mediastinitis gain prominence. Although treatment must be individualized, Dr. Santos demonstrated that transesophageal irrigation in such patients helps to clear the mediastinitis and save the esophagus and the patient.

Reference

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Sepsis and Tumor Necrosis Factor—Bedfellows that Cannot Be Ignored

A tremendous research effort has been expended by surgeons in the past half century to understand the mediators and modulators associated with severe infection. It has been reasoned that if the mechanisms underlying the hypotension, fluid sequestration, coagulation abnormalities, accelerated erosion of lean body mass, depressed immunity, impaired wound repair, and progressive tissue and organ damage could be defined, then therapeutic strategies could be developed to counteract these adverse events.

Nature has, however, been singularly reluctant to share with us these secrets. The afferent signals that initiate changes during critical illness are clearly active at concentrations close to the lower limits of detection, using the most sophisticated, state-of-the-art assay techniques. Furthermore, unlike conventional hormones, these signals often are generated locally within fixed tissues and initiate important alterations in the cells of origin or adjacent tissues without appearing in the circulation. Despite these limitations, 'mediator research' has described a number of important active molecules—for example we have now identified up to 10 interleukins and the list is growing. But how do we know which of these molecules is clinically significant? This fundamental issue was recognized many years ago by the great British physiologist, Sir Henry Hallett Dale, who commented, 'The discovery in artificial extract from an organ or tissue of a substance which on artificial injection produces a pharmacodynamic effect provides only a first item of presumptive evidence in support of a theory that the action of this substance plays a part in normal inflammation.'[1]

Tremendous enthusiasm is generated whenever novel mediators are characterized and this has been the case with the discovery of histamine, cortisone, and more recently fibronectin, interleukin-1, and many others. However, when the criteria originally proposed by Koch to demonstrate a relationship between an infective agent and a particular disease are applied, it has been difficult to argue convincingly for a major role for many of the more recently described mediators in critical illness. The single exception has been tumor necrosis factor (TNF/cachectin), a polypeptide product of activated reticuloendothelial cells, whose importance appears to be enhanced rather than diminished by the passage of time. In fact the criteria originally proposed by Koch have now been shown to be fulfilled by this cytokine, about which the following points can be made:

(1) It can be found in the circulation at the onset of critical infective illness. Early attempts to demonstrate TNF in the circulation were largely unsuccessful. However it has been recognized that the TNF signal appears as a short-lived pulse in the circulation and that the signal declines rapidly, frequently with the onset of symptoms. Circulating TNF has now been demonstrated during the prodome and at the onset of critical infective illness of many etiologies, and in selected infections, TNF concentrations will predict with remarkable accuracy whether death will occur.[2,3]

(2) TNF administration initiates alterations indistinguishable from those that occur after bacterial invasion. Administration of recombinant TNF to mammals induces death from circulatory collapse, renal failure, and disseminated intravascular coagulation. Autopsy findings are identical to those observed after severe gram-negative septicemia.[4] When TNF was infused into cancer patients in a phase 1 treatment protocol, the entire spectrum of changes associated with acute bacterial infection were observed, ranging from a mild flu-like illness to circulatory collapse and 'shock lung,' depending on the administered dose.[5] Sublethal TNF infusions in dogs also initiated the characteristic hormonal and metabolic abnormalities associated with sepsis.[6]

(3) TNF is one of the first mediators to appear during lethal infection. Multiple mediators are present in the circulation of the dying host and these include interleukin-1, interleukin-6, and products of the cyclooxygenase pathway. However the detection of TNF in the blood stream markedly antedates the appearance of all these other mediators in all appropriate experimental and clinical situations studied to date. Because TNF is known to stimulate the induction of many of the other mediators and pathways *in vitro,* there is a growing belief that TNF is the initial signal in lethal sepsis.

(4) Neutralization of TNF prevents death following lethal gram-negative bacteremia. Tracey and coworkers,[7] demonstrated that pretreatment of primates with a neutralizing monoclonal antibody against TNF prevents death following an otherwise lethal dose of virulent *Escherichia coli* organisms. Similar findings have been reported in other mammals.[8]

It is clear from the growing evidence that TNF plays a major role in the host response to infection and accounts for many of the deleterious effects of septicemia. Some individuals, however, have voiced concern about modifying the host response to infection; they fear that the administration of anti-TNF antibody may somehow render the host vulnerable because of potentially beneficial effects of this cytokine. Certainly TNF has been conserved more strongly during mammalian evolution than has insulin, suggesting that in some circumstances it may be beneficial, not detrimental. Various theories have been proposed for the existence of TNF, including the suggestion that it is an endogenous 'cyanide capsule' to eliminate wounded or infected members of the herd and thus ensure survival of the fittest. All of these theories remain speculative, but the bulk of evidence supports the belief that during critical illness the induction of TNF within the circulation is an essential factor in determining death.

The speed with which TNF research has advanced has been the result of close collaboration between surgeons, basic molecular biologists, pharmaceutical companies and human use committees. These interactions have allowed important research that focuses on the pathogenesis of critical illness to progress in a very short period of time. This collaboration will be even more necessary now that we have the pharmacologic tools to modify the basic signals involved in the mediation of infectious illness.

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Hepatic Abscess

Changes in Etiology, Diagnosis, and Management

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Most recent reviews of pyogenic hepatic abscess emphasize percutaneous *versus* open surgical management and devote little time to studying the etiology or the clinical condition of the patient. In this study a detailed review was performed with a computerized analysis of multiple clinical parameters in 73 patients treated for pyogenic hepatic abscess during a 17-year period. The mean age of the patients was 55 years and 38 of them (52%) were male. The mortality rate was comparable for solitary (17%) and multiple (23%) abscesses. The likelihood of death was higher with antibiotic treatment alone (45%) or percutaneous treatment (25%) than with surgical treatment (9.5%). The primary determinant of outcome, however, was the underlying disease, *i.e.*, malignancy or an immunocompromised patient, rather than solitary *versus* multiple abscesses. In addition the incidence of hepatic abscess seen at this center has doubled from the first half to the second half of the review, reflecting a population of more severely ill patients. It is apparent that in current clinical practice several methods of management are effective, and the choice of therapy should be determined by individualized selection. The principle of timely diagnosis and prompt institution of treatment appropriate to the specific patient remains the standard of care in this potentially grave disease.

PYOGENIC HEPATIC ABSCESS remains a major diagnostic and therapeutic challenge, despite advances in diagnostic technology and new strategies for treatment. While the incidence is reported to be stable, the question of increasing incidence of hepatic abscess and underlying malignancy, immunocompromise, or advanced age remains unanswered. The development of newer diagnostic methods, including ultrasound and computed tomography, has not only made the diagnosis more certain but also has introduced a range of treatment options. This report reviews an experience with nonparasitic hepatic abscesses during the past two decades. The study was undertaken to aid in the development of treatment strategies for hepatic abscess. The impact of a changing patient population, new diagnostic methods, and current therapy were assessed on the ultimate course of patients with hepatic abscess.

Methods

The records of patients with the diagnosis of hepatic abscess at Duke University Medical Center from 1970 to 1986 were reviewed. The historical record and physical examination were reviewed in detail, as were the types of diagnostic methods used, treatment, and results. Emphasis was placed on characteristics of the abscesses, including location and microbiology, primary and secondary treatment, complications, and survival time. Pyogenic hepatic abscess was defined as one or more discrete lesions in the liver in association with positive bacterial culture of material obtained at operation or percutaneous aspiration, or from blood or bile in the presence of an intrahepatic cavity observed on an imaging study. Patients diagnosed at operation or by radiologic study without a positive culture were included in the absence of another evident diagnosis. In two patients the diagnosis was made at autopsy. Patients with amoebic or other parasitic abscesses were excluded. Data was entered on detailed computer sheets and analyzed using a two-stage technique. The first stage consisted of computation of simple frequencies. The second included the cross-correlation of multiple variables, and chi square analysis was applied where appropriate.

Results

Demographic Information

The patients ranged in age from 3 to 85 years, with a median of 53 years. The peak incidence of hepatic abscess occurred in patients in the sixth decade (23%), but the

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distribution was roughly equal from the third decade forward. There were 38 male and 35 female patients. Twenty-eight patients were treated from 1970 to 1978 (11.5/100,000 admissions) while 55 were treated from 1979 to 1986 (22/100,000 admissions; Fig. 1).

The underlying pathologic findings changed with time. Benign biliary disease (*i.e.*, acute cholecystitis or choledocholithiasis) caused a lower proportion of cases after 1979, although the actual numbers were equal in both parts of the study (Table 1). The incidence of malignant colonic disease remained stable during the two decades. The number and relative incidence of underlying malignant biliary disease and benign colonic disease, including diverticulitis and appendicitis, increased between the first and second halves of the study.

Signs and Symptoms

Clinical and historical features were highly variable in this diverse group of patients and were associated primarily with the intra-abdominal infectious process (Table 2). Fever and/or chills (38%) and abdominal pain (36%) were the most common initial complaints. Anorexia and/or malaise was next, with bleeding being the initial problem in two patients, one having a percutaneous biliary drainage tube. The most common physical finding was a fever of more than 38 C (61%), followed by hepatomegaly (38%) and localized right upper quadrant tenderness (36%). Weight loss was documented in 31%, jaundice in 23%, with ascites apparent in only three patients (4%). No significant correlation was found between any particular symptom or symptom complex and the underlying disease, number or microbiology of the abscesses, or ultimate outcome.

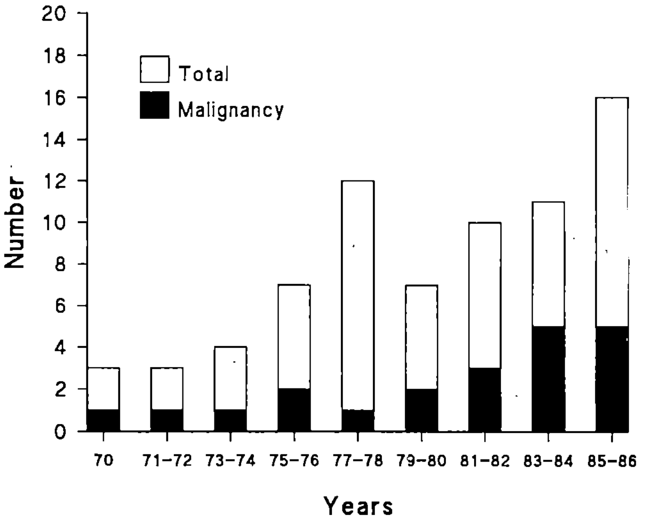

FIG. 1. Incidence of hepatic abscesses and underlying malignant neoplastic disease over time.

TABLE 1. *The Relative Incidence of Underlying Disease During the Review Period*

Underlying Disease	1970–1978 (n = 29) No. (%)	1979–1986 (n = 44) No. (%)
Biliary		
Benign	6 (21)	6 (14)
Malignant	3 (10)	6 (14)
Colonic		
Benign	2 (7)	7 (16)
Malignant	1 (3)	1 (2)
Hematologic	1 (3)	6 (14)
Cryptogenic	9 (31)	11 (25)

Laboratory

As expected, most patients (68%) had a leukocyte count of more than 10,000/mm^3 and 40% had more than 10% band forms. The alkaline phosphatase (78%) and serum glutamic oxaloacetic transaminase (SGOT) (57%) levels usually were elevated, while the bilirubin level was elevated in 36%. Two thirds of patients were anemic, due largely to chronic disease (Table 3). No single test or combination of tests were more predictive of outcome or significantly correlated with size or number of abscesses, complications, or time in the hospital.

Imaging Studies

The pattern of use of imaging studies changed significantly during the period of this review. Plain roentgenograms (n = 72) and sulphur colloid scanning (n = 31) were performed throughout the period of the study. Before 1974 all nine patients with a positive diagnosis underwent sulphur colloid scans. Between 1974 and 1979, 63% (14)

TABLE 2. *Signs and Symptoms*

Sign/Symptom	No.	%
Initial complaint		
Fever/chills	31	38
Abdominal pain	29	36
Anorexia/malaise	9	12
Symptoms		
Fever/chills	55	75
Anorexia/malaise	42	58
Abdominal pain	40	55
Nausea/vomiting	20	27
Weight loss	21	29
Night sweats	7	10
Diarrhea	6	8
Signs		
Fever (T > 38)	45	61
Hepatomegaly	28	38
RUQ tenderness	26	36
Weight loss	23	31
Right basilar rales	18	25
Jaundice	17	23
Diffuse abdominal tenderness	11	15
Ascites	3	4

TABLE 3. *Laboratory Data*

	No.	(%)
Hematocrit < 40 mg %	49	67
WBC > 10,000/mm	50	68
Bands > 10%	29	40
Alkaline phosphatase > 110 IU	57	78
SGOT > 35 IU/dL	42	57
Bilirubin > 1.5 mg/dL	26	36

WBC, white blood cell count; SGOT, serum glutamic oxaloacetic transaminase.

and 59% (13) of patients had ultrasound and liver/spleen scanning, respectively, and 45% (10) had both. In the period 1980 to 1986, 88% (37) of patients had CT scans, 48% (20) had ultrasound, while only 17% (17) of patients had sulphur colloid scans. There was little difference in the sensitivity of CT (100%), ultrasonography (84%), and liver–spleen scans (93%) in detecting abnormalities (Table 4).

Diagnosis

Clinical suspicion by physical findings, laboratory values, and the history leading to an imaging study was the most common route to diagnosis (88%). Six patients (8%) were diagnosed at operation, and two (3%) at necropsy. Seventeen patients each had positive cultures from material obtained from abscesses percutaneously or at operation. Of the six patients diagnosed at operation, two were explored for acute cholecystitis and one for appendicitis with incidental discovery of an hepatic abscess. Two pediatric patients, ages 3 and 10 years, underwent exploration without a diagnosis, one of whom had known hepatic fibrosis. One patient receiving chemotherapy for acute lymphogenous leukemia was explored for an epigastric mass that was found to be an abscess. Both patients diagnosed at autopsy died of underlying malignancy, one with acute granulocytic leukemia and the other with adenocarcinoma of the pancreas.

TABLE 4. *Hepatic Abscess Imaging Studies*

Study	No.	%
Chest roentgenogram (n = 72)		
Elevated right hemidiaphragm	12	16
Subdiaphragmatic air–fluid level	3	4
Subdiaphragmatic free air	2	3
Nonspecific abnormality	39	54
Abdominal roentgenogram (n = 38)		
Intrahepatic air	12	16
Ileus	12	16
Hepatomegaly	10	14
Intrahepatic air–fluid level	6	8
Air in biliary tree	4	6
CT scan (n = 42)		
Suspicious for abscess	31	74
Abnormal, nonspecific	11	26
Ultrasonogram (n = 37)		
Suspicious for abscess	31	86
No intrahepatic lesion	6	14
Sulphur-colloid scan (n = 31)		
Suspicious for abscess	14	45
Abnormal, nonspecific	15	48
Normal	2	7

CT, computed tomography.

Etiology

Benign and malignant disease of the biliary tract was the most commonly diagnosed underlying condition. Eight patients had malignant obstruction of the common bile duct, four with cholangiocarcinoma, three with pancreatic carcinoma, and one with carcinoma of the colon. Seven patients had abscess(es) associated with acute cholecystitis, including three with documented choledocholithiasis. Six patients had undergone biliary–enteric bypass procedures, four for chronic pancreatitis and two for pancreatic malignancy. Colonic disease contributed significantly to the series with four patients with diverticulitis, two with idiopathic or ischemic perforation, and one with Crohn's disease with perforation. Four patients had primary or recurrent adenocarcinoma of the colon, and four patients had hepatic abscess as a complication of appendiceal abscess or perforated appendicitis. A variety of other conditions contributed 15% of the cases, and 20 patients had no source identified (Table 5). Sixteen of these twenty patients underwent exploratory operation with no underlying cause found. Thirteen of the seventy-three patients had underlying organ malignancies. Seven had hematologic disease, including acute myelogenous leukemia in two patients and acute granulocytic leukemia, acute lymphogenous leukemia, idiopathic thrombocytopenia, erythroleukemia, and aplastic anemia in one patient each. Eight patients had diabetes mellitus, but only two patients

TABLE 5. *Underlying Disease*

Disease	No.	%
Biliary Disease		
Benign	12	16
Malignant	7	10
Colonic Disease		
Benign	11	14
Malignant	2	3
Hematologenous disease	7	10
Chronic granulomatous disease	4	5.5
Pancreatitis/ETOH	3	4.2
Trauma	2	3
Solid tumor—Other	2	3
Hepatic fibrosis	1	1.2
Ischemic bowel	1	1.2
Crohn's disease	1	1.2
Perforated ulcer	1	1.2
Cryptogenic	20	27
	73	100

in the cryptogenic group were diabetic. Five patients had underlying chronic granulomatous disease, one of whom also had appendicitis.

Gross Characteristics

Single abscesses were present in 43 patients (59%), and multiple abscesses were present in 30 patients (41%). Of some 110 total abscesses, 70% were in the right lobe. Eighty-six per cent of right lobe abscesses were solitary, while only 9% of left lobe abscesses were solitary. Fifty-two patients (73%) had at least one abscess measuring 3 cm or more in size. Benign conditions were the underlying cause of solitary lesions in 22 patients (56%) and multiple lesions in seventeen patients (44%). Single lesions were present in seven patients and multiple lesions were present in six patients in the 13 patients with underlying solid tumors. Hematologic disorders were associated with multiple abscesses in 83% of cases, while cryptogenic abscesses were solitary in 86%. There was no difference in the location of cryptogenic abscesses compared with the remaining patients of the group. The percentages of patients with biliary or colonic disease with regard to the location or number of abscesses was no different than in the group as a whole.

TABLE 6. *Microbiology*

Organism	Abscess	Blood	Bile	Other	Total
Gram-negative Aerobes					
Klebsiella	11	9			20
E. coli	10	9	2		21
Proteus	5	2			7
Pseudomonas	4	2	1	1	8
Enterobacter			1		1
Morganella	2	1	1		4
Serratia	1				1
Eikenella	1				1
Other GNR	2	1			3
Gram-positive Aerobes					
Enterococcus	6	2	1		9
Non-group D strep	4	2	1		7
Microaerophilic strep	4				4
Coagulase-Pos. Staph	3	2			5
Coagulase-Neg. Staph	3	1			4
Alpha hemolytic Stret	2	2			4
Gram-negative Anaerobes					
B. fragilis	7	4	1		12
Bacteroides species		1			1
Fusobacterium	4				4
Other GNR	1				
Other GNC	1				
Gram-positive Anaerobes					
Clostridia	3	1			4
Strep anaerobius	1	1			2
Peptostreptococcus	1				1
Actinomyces	1				1
Diptheroids		1			1
Gram-positive cocci	2				2
Fungal	2	2		1	5

TABLE 7. *Microbial Isolates in Single and Multiple Abscesses*

Isolates	No.	%
Solitary (43)		
Polymicrobial	27	63
Single Isolate	13	30
Fungal	0	0
None	3	7
Multiple (30)		
Single Isolate	11	37
Polymicrobial	9	30
Fungal	4	13
None	6	20

Microbiology

The first positive culture was obtained from one or more abscesses in 34 patients (47%) or from the blood in 23 patients (32%) (Table 6). Three patients had positive bile cultures following manipulations of the biliary tree, including percutaneous stenting (two patients), and common duct exploration for retained stones (one patient). One patient with multiple fungal abscesses had positive sputum only, and one patient had positive cultures obtained from the liver, spleen, and lung at autopsy. Nine patients (12%) who were treated with antibiotic therapy for various periods before obtaining cultures from any source had no positive cultures. Of 134 total isolates, 75% were aerobic (Table 6). *Escherichia coli* and *Klebsiella* were the most common bacteria, followed by *Bacteroides* species and enterococci.

Characteristics of single and multiple abscesses with regard to isolates are presented in Table 7. Solitary abscesses were more likely than multiple abscesses to be polymicrobial: 43 patients (63%) *versus* nine patients (30%). Aerobic isolates alone were found in 37 patients (51%) and pure anaerobic abscesses were found in only 8 patients (11%). All fungal isolates were Candida species and were found in patients with multiple lesions. Material from abscesses or from bile was more likely to yield positive cultures than was the blood.

Treatment

The pattern of treatment of hepatic abscess changed considerably during the period of this study (Fig. 2). From 1970 to 1978, 25 of 29 patients (86%) were treated first with operation, while from 1979 through 1986 equal numbers of patients had a surgical procedure or percutaneous drainage as the first definitive therapy. In total the first definitive therapy in solitary abscesses was surgical in 65%, percutaneous drainage in 26%, antibiotics alone in 7%, and staged percutaneous drainage followed by operation in 2%. Multiple abscesses were first treated by surgical drainage in 47%, percutaneous drainage in 29%, antibiotics alone in 23%, and staged percutaneous/surgical drainage in 7%.

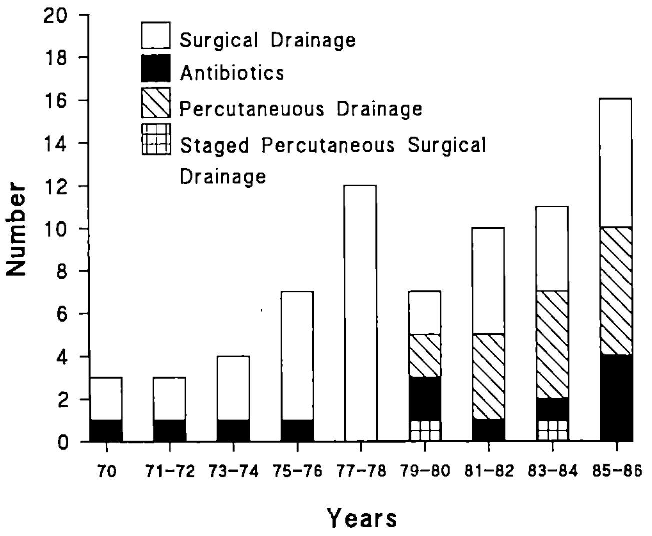

FIG. 2. Primary treatment of hepatic abscesses over time.

Complications were common, regardless of treatment, with 20 following operations (48%), 12 after percutaneous drainage (71%), and 8 after antibiotic therapy (73%). Reaccumulation of abscesses within 2 weeks after treatment occurred in eight (19%) patients after surgical drainage and seven (41%) following percutaneous drainage. Single- or multiple-system organ failure caused complications in two patients treated with percutaneous drainage and five patients following operation. Two patients treated with percutaneous drainage and five surgical patients had continuing sepsis, despite antibiotics. Three surgical and one percutaneous drainage patient developed ileus lasting at least 1 week after therapy. One surgical patient each developed pulmonary embolus, massive right pleural effusion, and an *E. coli* wound infection. Small bowel obstruction requiring surgical intervention occurred in two patients following initial surgical drainage. Antibiotic therapy with gentamicin caused acute renal failure in one patient and partial hearing loss in another after surgical drainage.

Secondary surgical procedures following earlier but inadequate drainage were performed in eight patients, five of whom had operations and three of whom had percutaneous drainage initially. One patient developed shock when percutaneous drainage of a solitary abscess of the right lobe was attempted, necessitating hemodynamic support and urgent surgical intervention. Percutaneous drainage was performed for initial failure or reaccumulation of an abscess after four percutaneous procedures, and one each of surgical and antibiotic failure. One patient with a solitary abscess in the right lobe required six manipulations or catheter exchanges during a period of 2 weeks before successful drainage was obtained.

Outcome

Fourteen patients in this series died, yielding a mortality rate of 19% (Table 8). The mean age of these patients was 53 years, which was not significantly different than the age of those who survived, and the distribution of deaths by decade was similar to the incidence of cases by decade. Seven each died with single (16%) and multiple (23%) abscesses. Seven of twenty patients (35%) with underlying malignancy died, while death occurred in only 7 of 53 patients (13%) with benign underlying conditions or unidentified causes. Multiple-system organ failure lead to death in five patients and sepsis superimposed on metastatic disease also was present in five patients. Three pa-

TABLE 8. *Mortality*

Year	Sex	Age	Underlying Disease	Number	Method of Diagnosis	Treatment	Complications
70	M	61	Pancreatic carcinoma	Single	Autopsy	Antibiotics	Sepsis, metastatic disease
72	M	51	Pancreatic carcinoma	Multiple	L-S scan	Antibiotics	Sepsis, metastatic disease
74	M	20	Acute granulocytic leukemia	Multiple	Autopsy	Antibiotics	Sepsis, immunosuppression
75	F	37	Colon carcinoma	Single	Celiotomy	Surgery	Abdominal abscess, metastatic disease
77	M	52	Pancreatic carcinoma, biliary bypass	Single	L-S scan	Antibiotics	Sepsis, metastatic disease
78	M	30	Pancreatitis, biliary bypass	Single	CT scan	Surgery	Sepsis, multiple-organ failure
80	F	81	ITP, steroid therapy	Multiple	CT scan	Surgery	Multiple-organ failure
80	M	52	Cholangiocarcinoma	Multiple	CT scan	Percutaneous	Multiple-organ failure
81	M	43	EtOH, ulcer perforation	Multiple	CT scan	Percutaneous surgery	Multiple-organ failure
82	F	52	Gangrenous cholecystitis, colon perforation	Single	CT scan	Surgery	Sepsis
83	M	63	Colon carcinoma	Single	CT scan	Percutaneous surgery	Sepsis, metastatic disease
85	F	63	Lupus, steroid therapy	Single	CT scan	Percutaneous	Sepsis, immunosuppression
86	F	81	Ischemic bowel	Single	CT scan Ultrasound	Antibiotics	Sepsis, DIC
86	F	50	Pancreatic CA, s/p Whipple	Multiple	CT scan	Percutaneous	Multiple-organ failure, metastatic disease

tients were immunocompromised from steroids or chemotherapy, and one patient had profound sepsis. Of the 14 deaths, 10 had polymicrobial infections, and no organism predominated among the group.

Underlying benign conditions leading to death included complications from biliary tract surgery for stones, diverticulitis, gangrenous bowel, perforated gastric ulcer, and two patients with exogenous steroids, one for idiopathic thrombocytopenia and one for systemic lupus erythematosis. No patient with a cryptogenic abscess died.

Discussion

In 1938 Ochsner and DeBakey[1] published the largest series of pyogenic abscess of the liver then in the literature. Their series included 139 cases of amoebic abscess and 47 cases of pyogenic abscess. This classic review emphasized the uniform rate of mortality of nonoperative treatment and the 95% mortality rate of multiple abscesses. The authors showed clearly in their review of the literature, as well as in their own series, the importance of primary abdominal disease and of portal venous drainage in the development of liver abscesses.

Many subsequent series, including those by Barber and Juniper,[2] and Lee and Block[3] emphasized the changing clinical patterns of hepatic abscess. One summary in 1975[4] noted a marked decrease in the incidence of appendicitis and other acute colonic diseases as sources of hepatic abscess.[5-7] An apparent increase in the age of patients occurred with effective treatment of various intra-abdominal disease processes in the younger patients. Despite changes in the epidemiology, the incidence has remained stable during the past five decades in this country, with six to ten cases per 100,000 admissions.[8-11]

The importance of biliary and colonic disease as an underlying source of contamination in a large percentage of patients is evident in this series, with 40% of patients with these sites as the source of infection. Despite diagnostic advances and aggressive evaluation in most cases, 27% of these patients had no underlying source identified, thus making cryptogenic abscess the largest single group in the study. Sixteen of the twenty patients with cryptogenic abscess underwent operative procedures for drainage of their abscesses, indicating that even direct visual and manual exploration does not guarantee identification of a source.

Of particular note in the present study was that 20 patients (27%) of this series also had an underlying solid malignancy or hematologic disease. Other reports included a growing population of immunosuppressed patients or those with malignant neoplastic disease.[4,12] In this subset of patients in the present study, only five presented from 1970 to 1978, while the remaining 15 patients presented between 1979 and 1986. The mortality rate in the group with malignancy was 35%, compared to 13% in patients with benign or cryptogenic conditions. This particular group now represents the largest group of patients with hepatic abscess and an identified concomitant illness. Therefore, considering all of the characteristics of the total group, malignancy was the most important determinant of outcome.

Early diagnosis remains important in the present series. Physical signs, symptoms, and laboratory evaluation have remained relatively unchanged with this disorder during the two decades. Clinical suspicion based on physical findings or complaints, along with abnormal laboratory tests leading to appropriate radiologic studies with confirmation were the most common means of diagnosis. Less than one third of patients in this series, however, had the complete symptom triad of right upper quadrant pain, fever or chills, and malaise. Indeed, in immunocompromised and elderly patients, a high index of clinical suspicion is necessary to initiate appropriate diagnosis.[13] Both ultrasound and CT scans were very sensitive to abnormality (86% and 100%, respectively), but even with recent technological advances, the literature continues to indicate a group of patients diagnosed only by operation or autopsy.[14,15] There were eight such patients (11%) in this series.

A review of the Duke series by McDonald et al.[16] ending in 1982 emphasized an evolving microbiology of pyogenic hepatic abscess. This was confirmed in other reports that identified an increase in the isolation of anaerobic and microaerophilic organisms.[17] This is thought to be secondary to improved culture techniques, as well as attention to detail in the collection of specimens. Pure anaerobic abscesses reportedly make up a small proportion of cases, indicating the importance of broad spectrum therapy if anaerobes are cultured. There may be a subset of patients with no diagnostic cultures obtained but who have received antibiotics. If hepatic abscess is the clinical diagnosis, but the contents and other cultures remain sterile, broad coverage with antibiotics necessarily continues for an adequate therapeutic course.

During the 18 years of this study, the mortality rate remained stable, 18% in the first 9 years and 16% for the following 8 years, despite a higher incidence of malignancy and hematologic disease during the latter period. In contrast to other series, the mortality rate was not related to age, multiplicity of lesions, or primary treatment (Fig. 3). After 1978 a marked change in the choice of primary therapy occurred, when percutaneous drainage became a useful adjunct to surgical drainage, as well as a primary therapeutic option.

Bertel et al.[18] emphasized the ease of treatment by percutaneous techniques, with successful results in as many as 83% of patients and morbidity as low as 20%. The most amenable abscesses to percutaneous drainage are those in

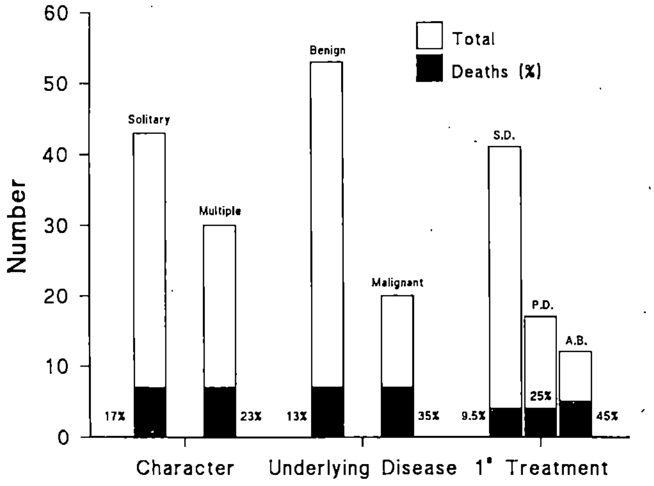

FIG. 3. Deaths secondary to hepatic abscess compared by character, underlying disease, and primary treatment. SD, surgical drainage; PD, 10 percutaneous drainage. AB, antibiotics alone.

the posterior right lobe, deep-seated lesions, and ones that are adherent to the abdominal wall. Superficial lesions or peripheral abscesses of the right lobe are easily treated by percutaneous drainage, and assuming no other intra-abdominal procedure is necessary, such drainage should be associated with fewer complications. Surgical therapy often remains necessary for abscesses of the left lobe or those that are multiloculated, or when this approach is advisable because of concomitant intra-abdominal disease. The determination of outcome of various therapeutic modalities of hepatic abscesses must include underlying conditions, location, and accessibility of the lesions. Raw comparisons of surgical *versus* percutaneous treatment are not appropriate without these considerations. As recommended in previous series,[4,12] antibiotic treatment alone should be a last resort, even considering the newer generation antibiotics.

In 1984 Miedma and Dineen[19] presented a series of 106 patients with pyogenic hepatic abscess and reported that despite easier diagnosis, the mortality rate remained high (53%). They also postulated that only 30 of their 106 patients would have qualified for percutaneous drainage, of which only three died. Following this presentation Nabseth[20] emphasized his previously reported series of 18 hepatic abscesses, 16 of which were successfully managed by percutaneous drainage with no deaths. Several subsequent series have been published comparing surgical to percutaneous treatment of hepatic abscess.[18,21,22] Percutaneous drainage clearly has emerged as an alternative in many patients with hepatic abscess.

A surgical procedure was the primary treatment in 28 patients with solitary and 14 patients with multiple abscesses. Six patients required further treatment because of inadequate drainage of the primary abscess, or occurrence of a secondary abscess. Percutaneous drainage was the primary treatment in 11 solitary and seven multiple cases. Four repeat percutaneous drainage procedures and three surgical drainage procedures were required (a 41% primary failure rate). The overall morbidity rate was 48% for operation and 71% for percutaneous drainage, including all major complications. These were prolonged ileus, small bowel obstruction, pulmonary embolus, pneumonia, pleural effusion requiring drainage, and recurrent abscess. It should be re-emphasized that percutaneous redrainage is usually a less morbid procedure than operative drainage.

Most surgical series cite morbidity rates in the range of 40%, with septicemia the most common complication.[4,15,18] Common pleural complications, include enlarging effusions, empyema, rupture into the right subphrenic space, and pneumonia. Other complications, such as bile duct obstruction, generalized peritonitis, and extrahepatic abdominal abscess are considerably less common. Percutaneous drainage complications are somewhat more difficult to define because of variability in the definition of complications between series. However most studies comparing surgical and percutaneous drainage quote complication rates of 40% to 60%.[23,24] This high incidence probably reflects the greater severity of illness in these patients. Crass[25] reported a high rate of acute sepsis with development of shock, ranging up to 25% either during or following the procedure. One patient in the present series required emergent operative intervention after percutaneous drainage when profound shock developed from peritoneal soilage by contents of the abscess. One patient died after percutaneous diagnostic aspiration without surgical consultation. These emphasize the importance of continued early surgical involvement with these patients.

This review re-emphasizes the findings of others[4,26] that successful treatment exchanges high mortality rates for high morbidity rates. The current therapy of pyogenic hepatic abscess should be individualized, with consideration of whether the abscess is solitary or multiple, whether additional problems requiring surgical therapy are present, and most significantly, the nature of the patient's underlying disease. McCorkel[27] recently proposed an evaluation of percutaneous aspiration followed by antibiotics as the primary therapy. Several immunocompromised patients in this series developed diffuse microabscesses not amenable to surgical or percutaneous drainage and were managed with antibiotics alone. Such patients had the highest mortality rate (45%) in this series and represent a special problem.

Some authors[12,28] advocate hepatic resection in cases of abscess localized to one lobe. Resection is probably most useful in selected cases of chronic granulomatous disease, although closed and open drainage are still important techniques.

Pyogenic hepatic abscess remains a difficult problem. Although relatively uncommon, its incidence is not decreasing and should be expected to increase with contemporary aggressive treatment of malignant disease. In the present experience death is more consistently related to the underlying disease and overall condition of the patient than to the mode of therapy chosen, *i.e.*, percutaneous *versus* surgical drainage. On the other hand, morbidity is more related to treatment. The principal of timely diagnosis and prompt institution of treatment appropriate to the individual patient remains the standard of care in this potentially grave disease and usually leads to a successful ultimate result.

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ORIGINAL ARTICLES

The Effects of Tumor Necrosis Factor on Intestinal Structure and Metabolism

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Tumor necrosis factor (TNF), a polypeptide produced predominantly by activated macrophages, is an important mediator of sepsis. We analyzed the specific metabolic changes that occur in the gut following TNF administration. Following general anesthesia, hemodynamic and metabolic indices were measured serially in control dogs (n = 7) and animals receiving a continuous sublethal intravenous infusion of TNF ($0.57.10^5$ IU/kg/6 hours, n = 7). During TNF infusion mean arterial pressure gradually decreased despite fluid administration, which maintained wedge pressure and cardiac index, which were similar to control animals. While TNF significantly reduced intestinal blood flow to 12 ± 3 mL/min/kg compared to 28 ± 3 mL/min/kg ($p < 0.01$) in controls, intestinal oxygen consumption was maintained due to an increased extraction rate. Despite hypoperfusion the intestinal exchange of metabolic substrate (glucose, lactate, pyruvate, alanine, glutamine, glutamate, and ammonia) was comparable between the control and TNF-infused animals. However, when substrate carbon balance across the intestinal tract was calculated, it appeared that there was a limitation in fuel availability in the TNF animals. This may be due to competition for fuel between the gut and other major organs. Fuel limitation may jeopardize rapid cell proliferation and mucosal repair and with regional hypoperfusion these processes may account for the mucosal ulcerations observed at the termination of the study.

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THE CATABOLIC RESPONSE to critical illness is characterized by a set of alterations in metabolism, including an increase in metabolic rate, an acceleration of skeletal muscle proteolysis and increased amino acid flux, negative nitrogen balance, and alterations of carbohydrate and fat metabolism. Previous studies suggest that the intestinal tract plays a central role in these metabolic alterations, particularly in the regulation of amino acid delivery from skeletal muscle to the liver.[1-3] Other investigations suggest that many of the responses that occur after infection are mediated, in part, by cytokines, and tumor necrosis factor (TNF) may be a major participant in this response.[4-8] With TNF administration, the hypothalamic-pituitary-adrenal axis is activated, protein metabolism is altered, and acute-phase changes occur.[8-11] Chronic TNF infusion causes an increase in liver mass as reflected by an increase in protein content and induces hypocellularity in the intestinal mucosa.[12] To further evaluate the effects of this cytokine on the gastrointestinal tract, we monitored exchange of substrate across the bowel during TNF infusion.

Materials and Methods

Study Design and Operative Procedure

Fourteen mongrel dogs of either sex, weighing between 22 and 34 kg, were obtained from an animal farm at least 3 weeks before the study. The animals were housed in accordance with the recommendations of the Committee on Animal Care of the Harvard Medical School.

To exclude the contribution of the spleen to the portal venous circulation, a splenectomy was performed in all dogs at least 2 weeks before the experiments. At that time, the splenectomized dogs were studied only if they satisfied strictly defined criteria that indicated full recovery.[1]

Dogs were allocated randomly to a control group (n = 7) or to a group receiving TNF (n = 7). After an overnight fast, anesthesia was induced with pentobarbital sodium (25 to 30 mg/kg administered intravenously; Nembutal, Abbott Laboratories, Chicago, IL); during the experiment intravenous Nembutal injections (50 mg at a

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time) were repeated to maintain light anesthesia. After endotracheal intubation, urinary catheter and rectal temperature probes were inserted. The dogs were allowed to breathe spontaneously a mixture of approximately 60% oxygen and air. Under sterile conditions, silicone catheters were inserted into the carotid artery and the external jugular vein. The carotid artery catheter was attached to a standard mercury manometer. A flow-directed triple lumen pulmonary artery Swan-Ganz catheter was inserted *via* the external jugular vein. The distal opening was connected to a pressure amplifier (Model CM; Honeywell, Inc., Pleasantville, NY). Into the jugular vein catheter, 0.9% saline was infused at a rate of 4 mL/kg/hour. The TNF-infused dogs needed additional 0.9% saline administered to maintain hourly measured wedge pressure. The abdominal cavity then was entered through a small midline incision. A silicone catheter was inserted into a mesenteric vein of the proximal small bowel and directed into the portal vein; its tip was located in the porta hepatis by palpation. Next a mesenteric infusion catheter was inserted into a mesenteric vein of the distal small bowel and advanced approximately 2 cm. Both catheters were exteriorized *via* the wound. During this procedure the bowel was only minimally handled. A solution of para-aminohippurate (PAH) sodium in 0.9% saline (0.5 g PAH/100 mL 0.9% saline) was constantly infused into the mesenteric infusion catheter at a rate of 0.36 mL/minute. After 90 minutes steady-state dye concentrations were achieved[13] and baseline measurements were performed. Subsequently, in selected animals, TNF (0.57×10^5 IU/kg body weight; Asahi Chemical Industry Inc., New York, NY) was infused peripherally during a 6-hour period.

Measurements

Vital signs were monitored hourly. Every 2 hours arterial, mixed venous, and portal venous blood samples were taken for blood gas analysis and total body oxygen consumption was measured by closed circuit respirometry. Cardiac output was calculated indirectly by the Fick method. At 3-hour intervals, arterial blood samples were obtained for determination of hematologic indices and concentrations of blood urea nitrogen and stress hormones (adrenalcortical tropic hormone [ACTH], cortisol, insulin, glucagon, and epinephrine). Every 3 hours simultaneous arterial and portal venous samples were obtained to determine concentrations of PAH, potassium, and various metabolic substrates (including glucose, lactate, pyruvate, glutamine, glutamate, alanine, and ammonia). Regional blood flow and substrate flux were determined as previously described.[3,13] Total carbon balance (expressed per liter of intestinal blood flow) was calculated as the sum of all carbons taken up or released by the gut *via* the exchange of these same substrates. Intestinal oxygen consumption was calculated by the reversed Fick method. Oxygen extraction and ammonia production (expressed per liter of intestinal blood flow) also were calculated. The intestinal redox state was estimated by calculating the portal venous lactate/pyruvate ratio.[14]

Aerobic and anaerobic blood cultures were taken from the portal venous catheters at the beginning and at the end of the study. Urine was collected during the 6-hour period and further analyzed for electrolytes and nitrogen products. Urea production (expressed per kilogram of body weight) was calculated from the 6-hour urine value corrected for changes in total body water and blood urea nitrogen concentration.

At the end of the study, all TNF-infused animals and five of seven control animals were killed by administering an overdose of anesthetic agent, and the positions of catheters were verified. The ligament of Treitz was identified and a point 30 cm from the ligament identified. Two 10-cm segments of jejunum were excised distal to this point. The segments were cleaned of fat, opened, and rinsed with chilled 0.9% saline. The proximal segment was blotted dry and weighed; it was then dried for at least 16 hours at 90 C and reweighed. The distal segment was diced, homogenized, and stored at −70 C until measurement of DNA and protein content. The same procedure was performed on two 5-cm proximal colon segments located 10 cm from the ileocecal valve.

Chemical Analysis

Whole blood concentration of PAH, glutamine, glutamate, alanine, and ammonia were measured as previously described.[15] Concentrations of stress hormones also were determined as previously described.[11] Tissue DNA content was determined using a modification of the method of Burton[16] and protein content was measured using Lowry's technique.[17] Standard analytical methods were used for the measurement of other substrates, electrolytes, and hematologic indices.

Data Analysis

Statistical calculations were performed on a personal computer (Tandy 1000 SX, Tandy Corp., Fort Worth, TX) using standard software packages (Ability Plus, Migent Inc., NV; Statgraphics, STSC Inc., Rockville, MD; SAS Software, SAS Institute, Cary, NC). Student's paired and unpaired t tests, repeated measures analysis of variance (ANOVA), and chi square test with Yates' correction were used when appropriate. Results are expressed as mean ± the standard error of the mean (SEM). Differences were considered significant when $p < 0.05$.

Results

Systemic Response

Anesthesia dose was similar in both groups of animals (control group: 41.1 ± 3.1 mg pentobarbital/kg body weight *versus* TNF group: 36.0 ± 1.7 mg/kg body weight). Body temperature increased during the 6 hours of study in both groups of animals and the increase was comparable (from 38.1 ± 0.2 C to 40.2 ± 0.1 C in the control group and from 38.7 ± 0.1 C to 40.5 ± 0.2 C in the TNF group). Both groups developed a tachypnea (from 16 ± 1 to 28 ± 6 breaths/minute in the control group and from 17 ± 2 to 46 ± 5 breaths/minute in the TNF group), which was significant by 4 hours and persisted at 6 hours; no differences were observed between the two groups.

While mean arterial pressure was stable throughout the 6-hour study in control dogs, blood pressure decreased to approximately 80 mmHg by 6 hours in the dogs receiving TNF (Fig. 1). Despite this decrease in mean arterial pressure, the TNF dogs developed a relative bradycardia; at 6 hours their heart rate was significantly lower in comparison to the controls. Cardiac index fell significantly during the first 2 hours of the study period in both groups (Fig. 1) and then stabilized. No significant difference occurred between the two groups.

To maintain a constant wedge pressure, additional fluid was administered to all seven dogs receiving TNF; this ranged in volume from 400 to 1000 mL 0.9% saline/6 hours (mean = 779 ± 84 mL/6 hours). In both groups of animals the hematocrit decreased significantly during the 6 hours (from 44% ± 2% to 39% ± 2% in control animals and from 46% ± 2% to 40% ± 2% in TNF-treated animals; $p < 0.01$); no differences were observed between the two

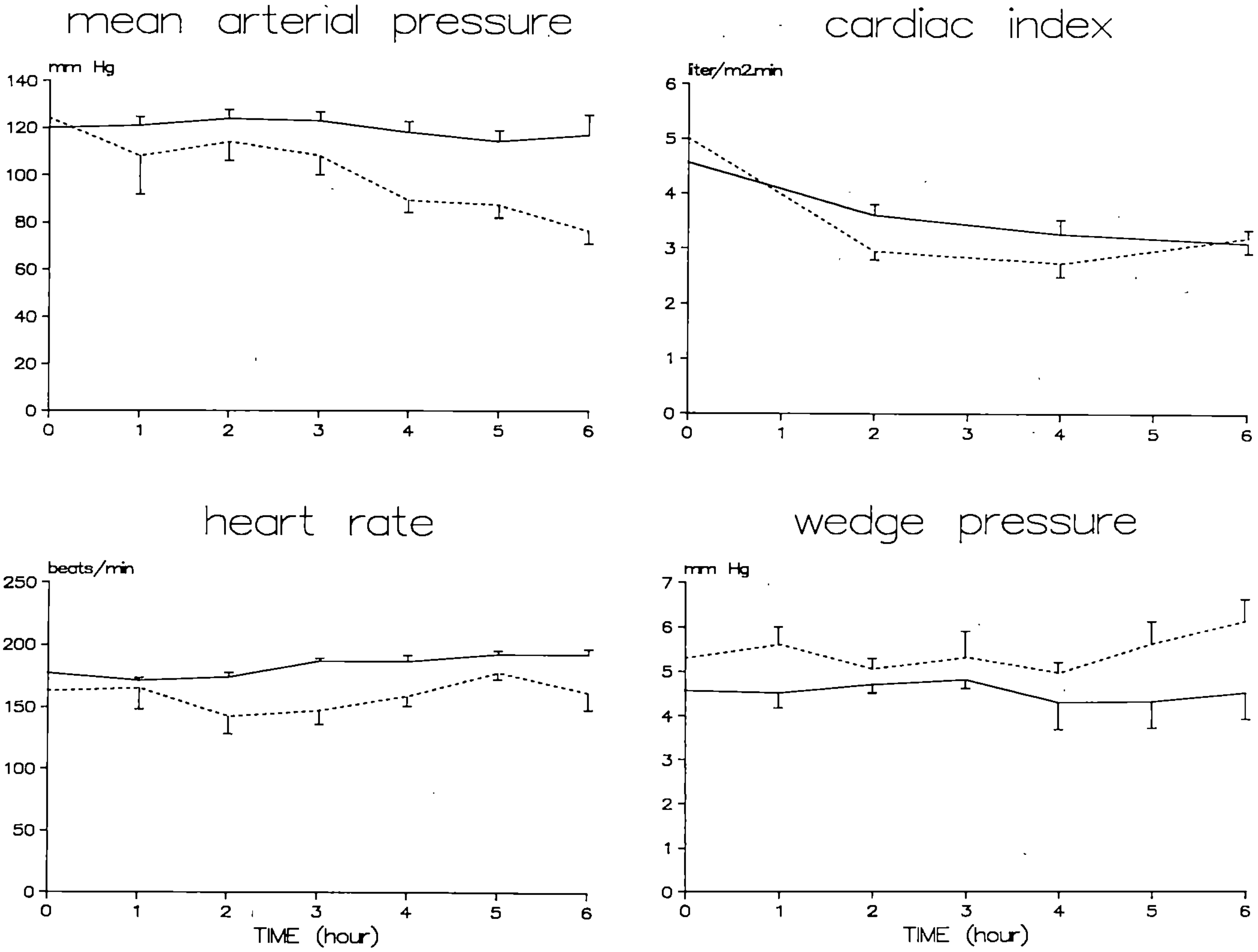

FIG. 1. Hemodynamic changes during 6 hours in control animals (solid lines) and in TNF-infused animals (dashed lines).

TABLE 1. *Arterial Substrate Concentrations and Base Excess (BE) Values in Control and TNF-infused Animals*

Substrate		Time (hours) 0	3	6	Change
Glucose	Control	0.84 ± 0.04	0.91 ± 0.04	0.99 ± 0.07	↑ *
[mg/mL]	TNF	0.84 ± 0.02	0.76 ± 0.03	0.70 ± 0.04	↓ *
Lactate	Control	1.29 ± 0.28	1.16 ± 0.18	1.10 ± 0.23	– NS
[mmol/L]	TNF	1.11 ± 0.23	1.71 ± 0.24	2.20 ± 0.34	↑ †
Base Excess	Control	−4.5 ± 0.9	−3.5 ± 0.8	−3.3 ± 0.9	– NS
[mEq/L]	TNF	−2.9 ± 0.7	−5.5 ± 0.8	−8.0 ± 0.9	↓ †
Pyruvate	Control	91 ± 19	93 ± 14	94 ± 17	– NS
[μmol/L]	TNF	67 ± 16	110 ± 11	129 ± 14	– NS
Glutamine	Control	548 ± 24	600 ± 31	633 ± 53	– NS
[μmol/L]	TNF	643 ± 26	616 ± 25	691 ± 39	– NS
Alanine	Control	324 ± 40	342 ± 58	344 ± 51	– NS
[μmol/L]	TNF	310 ± 23	398 ± 20	605 ± 59	↑ †

↑, significant increase over time; ↓, significant decrease over time; –, no change over time; *$p < 0.05$, †$p < 0.01$.

groups. White blood cell count increased significantly in control dogs from 17.0 ± 1.9 × 10^9/L at the start to 30.1 ± 3.7 × 10^9/L after 6 hours ($p < 0.01$); in the TNF-treated dogs it decreased significantly from 14.4 ± 2.7 to 6.4 ± 1.5 × 10^9/L ($p < 0.05$).

Arterial glucose concentration increased significantly in the control dogs, while it decreased in the TNF-treated dogs (Table 1). In control animals the arterial lactate concentration and base excess did not change, but lactate increased and base excess decreased in the TNF group such that significant differences were present between groups at 6 hours. At this time arterial pH was significantly lower in the TNF group as compared to controls (7.27 ± 0.03 *versus* 7.34 ± 0.02, $p < 0.05$). Arterial concentrations of pyruvate and glutamine were not significantly different for the two groups. In the TNF-treated dogs, the arterial alanine concentration increased with time but remained unchanged in controls. At 3 hours and at 6 hours, arterial concentrations of ACTH, cortisol, glucagon, and epinephrine all were significantly greater in the TNF-infused animals (Table 2). No significant differences in urine volume and urinary electrolyte and nitrogen excretion were observed between control and TNF-treated animals (Table 3). Urea nitrogen generation also was similar in the two groups (90 ± 11 *versus* 102 ± 4 mg/kg/6 hours).

Hemodynamic and Metabolic Changes in the Gut

While intestinal blood flow remained unchanged in control dogs, it decreased significantly in the animals receiving TNF and differences were observed between the two groups of animals at 3 and 6 hours (Fig. 2, $p < 0.05$). Intestinal oxygen consumption rose significantly with time (Fig. 2, $p < 0.05$), but no differences occurred between the two groups. Despite the decrease in intestinal blood flow with TNF infusion, the intestinal redox state (expressed as portal venous lactate/pyruvate ratio) was not significantly altered and tended to decrease with the TNF infusion (18.25 ± 2.06 initially *versus* 14.83 ± 0.48 at 6 hours).

No difference in intestinal flux of metabolic substrates was observed between the two groups (Table 4). Intestinal oxygen extraction rate (expressed as the number of mil-

TABLE 2. *Arterial Concentrations of Stress Hormones in Control and TNF-infused Animals*

Hormones		Time (hours) 0	3	6
ACTH	Control	136 ± 21	29 ± 6	25 ± 8
[pg/mL]	TNF	128 ± 24	366 ± 67†	701 ± 195†
Cortisol	Control	8.6 ± 0.8	5.3 ± 0.6	5.8 ± 1.3
[μg/dL]	TNF	8.5 ± 1.2	11.6 ± 1.3†	10.7 ± 1.0*
Insulin	Control	10.5 ± 1.9	6.7 ± 1.2	7.2 ± 0.9
[IU/mL]	TNF	8.7 ± 2.2	6.0 ± 2.7	3.1 ± 1.5*
Glucagon	Control	418 ± 64	418 ± 55	471 ± 64
[pg/mL]	TNF	395 ± 36	700 ± 77*	1489 ± 108†
Epinephrine	Control	679 ± 252	295 ± 86	640 ± 248
[pg/mL]	TNF	408 ± 260	724 ± 176*	1751 ± 462*

* $p < 0.05$, †$p < 0.01$ *vs.* controls.

TABLE 3. *Urine Volume and Urinary Excretion of Different Substances in Control and TNF-infused Animals*

Urine Measurements	Control	TNF
Urine volume [mL/kg/6 hrs]	5.0 ± 1.3	9.6 ± 2.3*
Sodium [meq/kg/6 hrs]	0.43 ± 0.24	0.90 ± 0.31*
Potassium [meq/kg/6 hrs]	0.66 ± 0.13	0.87 ± 0.13*
Total N [g/kg/6 hrs]	0.13 ± 0.02	0.10 ± 0.01*
Urea N [mg/kg/6 hrs]	111 ± 14	90 ± 2*
Creatinine [g/kg/6 hrs]	0.008 ± 0.001	0.008 ± 0.001*

* $p > 0.05$ *vs.* controls.

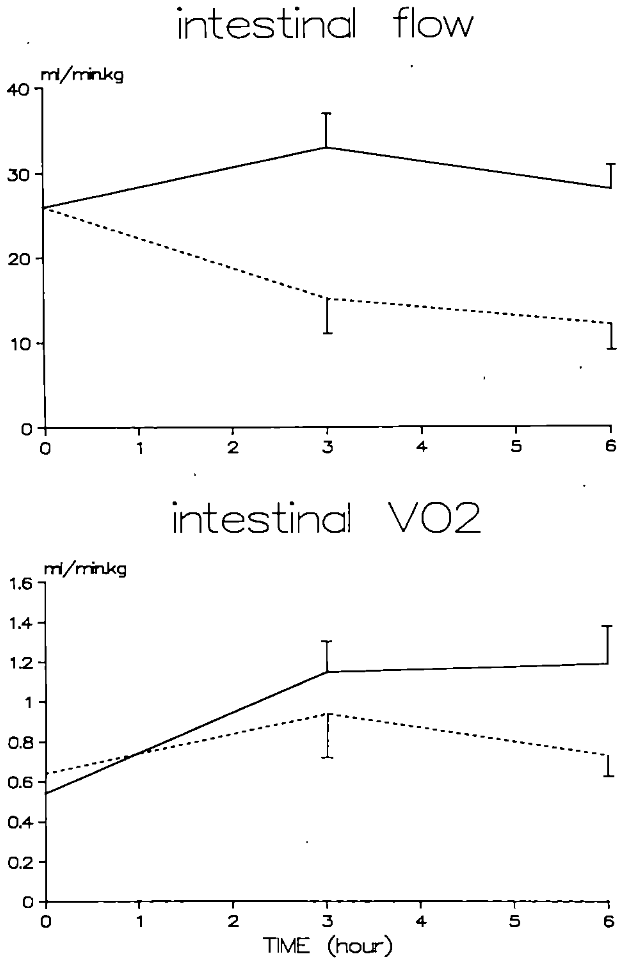

FIG. 2. Alterations of intestinal blood flow and intestinal oxygen consumption (VO2) during 6 hours in control animals (solid lines) and in TNF-infused animals (dashed lines).

liliters of oxygen extracted per liter of blood circulating through the gut) and intestinal ammonia production rate (expressed as micromoles of ammonia released to 1 L of blood circulating through the gut) were significantly higher in the TNF-treated group as compared to controls (Table 5, $p < 0.01$ and $p < 0.05$, respectively). Total carbon extraction rate (expressed as net micromoles of carbon extracted per liter of blood *via* the exchange of glucose, lactate, pyruvate, glutamine, glutamate, and alanine), however, was not statistically different between the two groups. The potassium flux did not change significantly during time in the two groups; nor was any significant difference in potassium flux detected between the two groups (data not shown).

Structural and Functional Aspects of the Gut

Six of the seven TNF-infused animals had focal, submucosal small bowel infarctions at autopsy, which were most pronounced in the distal ileum. Mesenteric and portal venous thrombosis were not present in these animals. None of the five control dogs that underwent autopsy showed comparable small bowel lesions. No gross pathologic lesions were found in the liver, kidney, and adrenal glands. Pulmonary atelectasis was observed frequently in both groups of animals. These lesions could be macroscopically reversed by overinflation of the lungs.

Jejunal and colonic dry weight:wet weight ratios were similar in the TNF-infused and control groups (jejunal segment: 0.20 ± 0.01 *versus* 0.20 ± 0.00; colonic segment: 0.20 ± 0.01 *versus* 0.19 ± 0.01). Jejunal and colonic DNA/protein ratios also were unchanged after TNF infusion (jejunal segment: 0.065 ± 0.007 *versus* 0.060 ± 0.001; colonic segment: 0.034 ± 0.004 *versus* 0.041 ± 0.003), suggesting that no change in intestinal cellularity occurred during this 6-hour study.

Before the commencement of the study, positive portal venous blood cultures were found in two of six control dogs and three of the seven TNF-infused dogs (chi square test, not significant [NS]). At the end of the study one of the six control dogs and three of the seven TNF-infused dogs had positive blood cultures (chi square test, NS).

Discussion

The purpose of this study was to examine the metabolic effects of TNF infusion on the gastrointestinal tract and not the effects of shock and death. Others have demonstrated that there is major disruption of the intestinal mucosa associated with lethal doses of TNF administered by intraperitoneal bolus injection.[9] In this study a sublethal infusion of TNF induced mild hemodynamic, metabolic, and endocrine changes similar to those previously reported from this laboratory in other canine studies.[11,18] Mean arterial blood pressure decreased from 124 to 76 mmHg in the TNF-infused animals and this was associated with a corresponding decrease in portal blood flow from 26 to 12 mL/min/kg (approximately 54%). In response to the decrease in intestinal perfusion, oxygen extraction increased, oxygen consumption normalized, and aerobic metabolism was preserved. This was confirmed by the intestinal production of lactate and pyruvate, which was similar in the TNF-infused animals to that of the control group (Table 4).

These responses are at variance with the alterations in intestinal blood flow that occurred during controlled hemorrhagic hypotension in the dog.[19] When mean arterial pressure was reduced from 130 to 60 mmHg, by volume depletion portal blood flow decreased approximately 59% (from 309 to 127 mL/minute), changes that

TABLE 4. *Intestinal Flux of Different Metabolic Substrates in Control and TNF-infused Animals*

Substrate		Time (hours) 0	3	6	Group Effect
Glucose	Control	1.25 ± 0.31	1.22 ± 0.38	1.33 ± 0.38	NS
[mg/kg/min]	TNF	1.18 ± 0.49	1.10 ± 0.29	0.72 ± 0.13	
Lactate	Control	1.40 ± 1.54	1.82 ± 1.90	−2.45 ± 1.14	NS
[μmol/L/kg/min]	TNF	1.88 ± 1.65	−0.55 ± 0.85	−4.28 ± 1.65	
Pyruvate	Control	0.45 ± 0.18	0.36 ± 0.15	0.06 ± 0.14	NS
[μmol/L/kg/min]	TNF	0.36 ± 0.32	−0.23 ± 0.09	−0.50 ± 0.14	
Glutamine	Control	0.94 ± 0.70	2.33 ± 0.48	2.60 ± 0.97	NS
[μmol/L/kg/min]	TNF	1.99 ± 0.52	1.81 ± 0.39	1.48 ± 0.34	
Glutamate	Control	−0.09 ± 0.03	−0.19 ± 0.06	−0.22 ± 0.05	NS
[μmol/L/kg/min]	TNF	−0.18 ± 0.07	−0.14 ± 0.04	−0.14 ± 0.01	
Alanine	Control	−0.63 ± 0.21	−0.85 ± 0.59	−0.55 ± 0.27	NS
[μmol/L/kg/min]	TNF	−1.09 ± 0.49	−0.74 ± 0.26	−0.88 ± 0.24	
Ammonia	Control	−86 ± 21	−135 ± 16	−160 ± 23	NS
[μg/kg/min]	TNF	−128 ± 39	−164 ± 44	−126 ± 14	

NS, not significant.

− flux indicates release; + flux indicates uptake. Differences between the groups (group effects) were analyzed by repeated measures ANOVA.

were similar to that observed in our animals. However, with hemorrhagic shock, intestinal oxygen consumption decreased from 19.0 to 12.7 mL/minute. While the hemodynamic changes were similar to those in our study, the changes in oxygen consumption were different for the TNF-infused animals, which maintained intestinal oxygen consumption between 25 to 30 mL/minute, a value similar to controls. It appears that these two quite varied stimuli result in different intestinal responses. It is possible that differences in anesthetic technique or a greater decrease in blood pressure (to a mean arterial pressure of 60 mmHg in the hemorrhagic shock model *versus* 76 in the TNF-infused dogs) could explain these differences.

In contrast to dogs undergoing hemorrhagic shock, endotoxin administration to dogs resulted in a decrease in blood pressure, a decrease in portal blood flow, and an increase in total resistance of the splanchnic bed.[20] At the same time there was an increase in intestinal weight and augmented sensitivity of small mesenteric veins to epinephrine. This observation formed the basis for the hypothesis that splanchnic sequestration of plasma occurred during septic shock and that this loss of circulating volume contributed to the associated hypovolemia and hypotension associated with sepsis. Tumor necrosis factor is thought to mediate the responses to endotoxin,[7–9] but similar changes in fluid sequestration were not observed in this study. The dry weight:wet weight ratio was similar in the TNF-infused and control animals, demonstrating that sequestration of fluid did not occur in the present study. In addition the arterial and portal venous hematocrit was monitored serially throughout the study, and no significant hemoconcentration occurred across the gut in any animals studied (data not shown). Thus it appears that the gut insult in this study was mild and compensatory adjustments were made to maintain bowel metabolism in the face of a decreasing portal blood flow. The alterations that occurred after the administration of endotoxin also have been observed with administration of greater doses of TNF resulting in lactic acidosis, hypotension, and death.[9]

TABLE 5. *Intestinal Oxygen and Carbon Extraction Rate and Ammonia Production Rate*

Extraction or Production Rate	Group Studied	Time (hours) 0	3	6	Group Effect
O2-Extraction rate	Control	22.4 ± 3.4	36.4 ± 2.8	40.4 ± 2.9	$p < 0.01$
[mL/L]	TNF	21.0 ± 3.2	63.1 ± 7.3	60.7 ± 4.4	
NH3-Production rate	Control	−192 ± 22	−250 ± 29	−336 ± 37	$p < 0.05$
[μmol/L]	TNF	−263 ± 34	−609 ± 121	−643 ± 104	
C-Extraction rate	Control	1972 ± 405	1587 ± 499	1725 ± 439	NS
[μmol/L]	TNF	1725 ± 392	2690 ± 357	1353 ± 592	

NS, not significant.

Values are means ± SEM and are expressed per liter of blood circulating through the gut.

Despite this fact mucosal lesions did occur in the TNF-infused animals, and these changes must have been related to specific microvascular hypoperfusion and/or cellular alterations, as have been described by others. Following TNF administration there is local release of secondary mediators such as platelet-activating factor, which results in bowel necrosis.[21] In addition, Fink and associates found that the intramucosal pH of the ileum of pigs decreased significantly during endotoxin administration. They concluded that alterations in microvascular blood flow could account for these alterations in cellular metabolism.[22]

One aim of this study was to investigate the alterations in intestinal fuels that occurred during TNF administration. It has been demonstrated previously that the stress of a simple uncomplicated laparotomy results in the increased extraction and uptake of the amino acid glutamine, a major respiratory fuel of the enterocyte.[1] It was an unexpected finding to note that the consumption of two primary substrates, primarily glutamine and glucose, generally was unaltered by TNF administration (Table 4). The intestinal tract, however, is one of several organs in competition for metabolic fuels, and regional adjustments in substrate consumption occur to aid host survival. For example the gut normally consumes some glucose, but during the hypoglycemia associated with TNF infusion the intestinal tract tended to diminish glucose consumption, presumably to spare glucose for other tissues (such as the central nervous system) that are obligate glucose consumers. Under other circumstances the intestine decreases glucose use and increases glutamine consumption.[23] However TNF infusion also was associated with a mild metabolic acidosis; a decrease in pH and base excess also occurred. During acute metabolic acidosis, there is competition for glutamine between the intestinal tract and the kidneys. Glutamine consumption by the intestinal tract remains constant while extraction and use of glutamine by the kidneys is accelerated greatly.[24,25] This occurs as the kidney generates additional ammonium ion, which is excreted in the urine. Concomitantly the kidney generates bicarbonate, which serves to buffer the acid load.

In the present study, TNF infusion resulted in mild hypoglycemia and the consumption of glucose by the bowel, probably a concentration-dependent process, tended to decrease. Glutamine then should be available to provide the additional fuel, but its use was limited because of the acute metabolic acidosis. Thus availability of metabolic fuel was tenuous in the TNF-infused animals. Despite the decrease in gut blood flow there was an increase in oxygen extraction. However this was not associated with an increased extraction of carbon substrate (Table 5), suggesting that delivery and use of metabolic substrate rapidly was becoming rate limiting. We do not know the effects that this metabolic environment may have exerted on the intestinal mucosa. Chronic TNF infusions in rats resulted in decreased mucosal cellularity, despite adequate nutritional support.[12] In this study DNA analysis revealed that significant cell breakdown had not occurred during 6 hours, but with time this may have occurred. Macroscopically mucosal damage had already occurred, possibly reflecting regional perfusion changes and limitation in fuel availability.

During sepsis and cytokinemia, the intestinal barrier defense mechanisms may become ineffective and allow bacterial invasion. In this study TNF infusion tended to increase the frequency of portal venous bacteremia, but the number of animals studied is too small to draw any definite conclusions from this data.

Sublethal TNF infusion induced a significant decrease in intestinal blood flow. Under these circumstances intestinal oxygen consumption and intestinal redox state remained unaffected, indicating that oxygenation of the gut generally was preserved. However carbon balance across the gut was diminished with time, suggesting a limitation in fuel availability. This may occur because of competition between the intestine and other organs for both glutamine and glucose. The intestine is thus placed in a tenuous position; regional hypoperfusion and fuel limitation may jeopardize maintenance of normal mucosal cellularity. These alterations may, in part, account for the mucosal ulceration observed at the end of this 6-hour study and explain the progressive deterioration of intestinal structure and function described by others.

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The Effect of Ambulation on Recovery from Postoperative Ileus

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To determine whether ambulation hastens recovery from ileus following laparotomy, 34 patients were studied, 10 of whom followed an ambulatory regimen beginning on postoperative day 1 (group A). The other 24 patients (group C) did not become ambulatory until postoperative day 4. All patients underwent placement of seromuscular bipolar recording electrodes on the Roux limb, if present, stomach, jejunum, and colon at laparotomy. Group A was recorded before and after ambulation so comparisons could be made to determine if ambulation had an acute effect on myoelectric activity. Group A preambulation and group C recordings were compared to judge whether there was an overall effect of ambulation on myoelectric recovery. No effect on slow wave frequency or percentage of slow waves with associated spike potentials was noted acutely or overall in the stomach, colon, or jejunum in continuity with the duodenal pacemaker. Transient increases in phase II spike activity in patients having a Roux limb and their jejunum distal to the enteroenterostomy were noted on postoperative days 1 to 2, but these differences resolved by postoperative days 3 or 4. The data suggest that ambulation as a means to help resolve postoperative ileus and its accompanying cramps and bloating may be more perceived than real.

EARLY AMBULATION FOLLOWING major abdominal surgery has come into general practice only recently. One of its earliest mentions in the medical literature was by Dr. Ephraim McDowell in an 1817 issue of the *Eclectic Repertory*.[1] At that time only a few physicians allowed their patients to ambulate within the first few days after surgery. It was not until the 1940s, after the publication of a series of articles by Daniel J. Leithauser, that early ambulation became a commonly accepted practice.[2,3] In many papers published then and since,[1,4] the benefits of early postsurgical ambulation have been realized and the metabolic, mental, and economic disadvantages of prolonged bedrest have become known. The problems facing the acceptance of early ambulation included the weight of tradition and the fear of poor wound healing that dictated prolonged postoperative bed rest. Personal experience and anecdotes were used by many to argue in favor of or against the practice.

One of the problems encountered by most surgical patients undergoing celiotomy is gastrointestinal ileus and the inability to take oral nourishment for 4 to 5 days or more. Generally it is believed that early ambulation aids in the restoration of normal bowel function, allows patients to more easily pass flatus and stool, and resume normal bowel habits. Patients are encouraged to walk for their overall well-being but also in an effort to resolve more quickly ileus and to relieve the associated cramps and bloating. This study was conducted to determine whether there is any evidence from gastrointestinal myoelectric activity data to substantiate this belief.

Methods

Thirty-five patients undergoing abdominal surgery participated in this study. Operative procedures included gastric bypass for morbid obesity, partial gastrectomy, abdominoperineal resection, exploratory laparotomy, and pancreaticojejunostomy for chronic pancreatitis. Vagotomy was not included in the surgical procedure in any of these patients. Informed voluntary consent was obtained from each patient under guidelines of the University of Virginia Human Investigation Committee.

At the time of laparotomy, pairs of 28-gauge stainless steel cardiac pacing wires were placed 1 cm apart to serve as bipolar recording electrodes in the seromuscular layer

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of the gastric fundus and body, jejunum, and transverse colon (Fig. 1). In patients with Roux limbs, electrode placement included the jejunum in continuity with the duodenal pacemaker (J1J2), the Roux limb (R1R2), and the jejunum distal to the enteroenterostomy (J3J4) (Fig. 2). Wires were brought percutaneously through the anterior abdominal wall and placed under a sterile dressing until they were needed for recording.

Myoelectric recordings were performed on fasting patients as their conditions permitted daily on postoperative days 1 to 3, 4 or 5, then every other day until discharge, and again at 1 month. Recordings were made using a modified Sensor Medics 8-channel dynograph recorder (Model R611; Sensor Medics Corp., Anaheim, CA) or a Hewlett Packard model 7758B recorder with 8811A bioelectric amplifiers and a 3960 instrumentation recorder (Hewlett Packard, Palo Alto, CA).

Patients were assigned randomly to one of two groups. Ten patients (group A) followed an ambulatory regimen starting 12 to 24 hours after operation and the other 25 patients served as controls (group C) and did not ambulate until postoperative day 4. Patients in group A underwent an initial 30- to 45-minute recording session, which was immediately followed by ambulation with assistance. Then they underwent another 60- to 90-minute postambulation recording session. Patients attempted to walk at least 75 yards during the ambulation session, but the distance varied with each patient's condition. Most patients achieved the desired distance. Group A patients also were allowed *ad libitim* ambulatory privileges when not being recorded. Group C patients underwent one daily continuous 90-minute recording session without ambulation or interruption. Group C patients did not ambulate outside their hospital room on any consistent basis for the first 4 days after laparotomy.

Recordings were analyzed for slow wave frequency, presence of migrating myoelectric complexes (MMC), amount of spike activity in phases II and III, and presence of colonic discrete and continuous electric-response activity patterns. Daily data from patients in group A were analyzed, comparing activity before and after ambulation to determine if any acute effect secondary to ambulation was present. The data collected before each day's course of ambulation were compared to the control group's data (group C) to identify any overall effect of early ambulation. Data from the stomach and small intestine were grouped together on days 1 to 2, 3 to 4, 5 to 7, and then at 1 month to provide adequate data points during each time period.

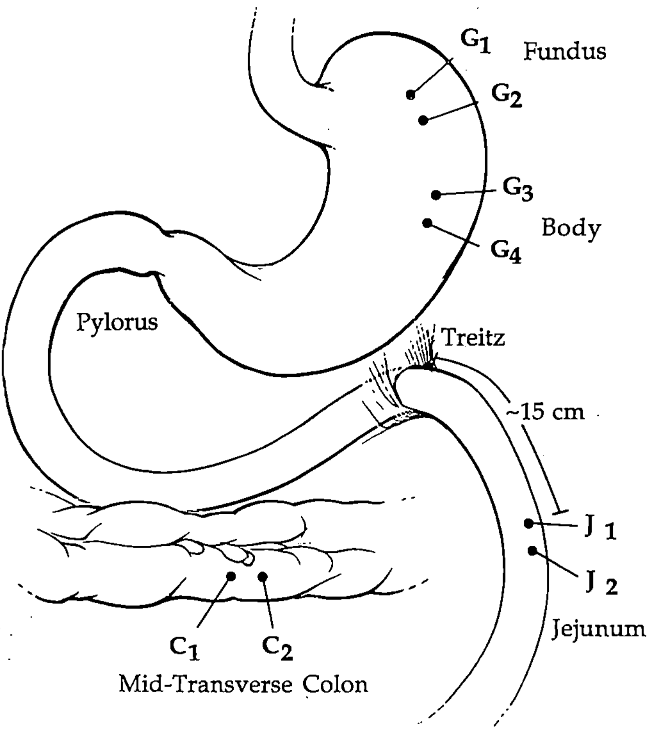

FIG. 1. Placement of seromuscular bipolar myoelectric recording wires in patients without a Roux limb.

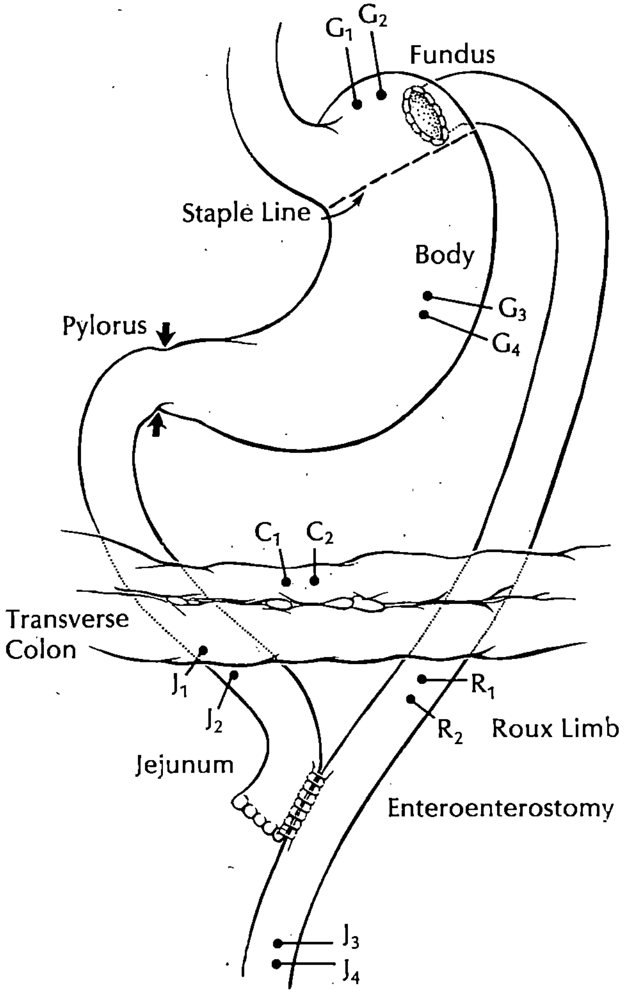

FIG. 2. Placement of seromuscular bipolar myoelectric recording wires in patients with a Roux limb.

TABLE 1. *Stomach Slow Waves (per minute)*

Day	1–2	3–4	5–7	1 Month
Preambulation				
Fundus	3.04 ± 0.09	2.99 ± 0.12	2.82 ± 0.09	2.74 ± 0.12
Body	3.06 ± 0.10	3.08 ± 0.10	2.96 ± 0.08	2.86 ± 0.07*
Postambulation				
Fundus	3.19 ± 0.11	3.09 ± 0.17	2.67 ± 0.07	—
Body	3.22 ± 0.11	3.07 ± 0.12	2.81 ± 0.07	—
Control				
Fundus	3.14 ± 0.14	2.89 ± 0.15	2.85 ± 0.08	3.30 ± 0.25
Body	3.09 ± 0.09	3.25 ± 0.12	3.03 ± 0.06	3.17 ± 0.11

* $p < 0.025$ compared to control group.

—, Results not applicable at 1 month.

Recordings at 1 month were thought to represent the patient's baseline state. Colon slow wave activity was pooled and grouped from days 1 to 4, 5 to 7, and at 1 month. The division between days 4 and 5 was chosen to provide adequate samplings of each slow wave frequency and because it is at about this time that normal colon myoelectric activity returns and clinical symptoms indicating return of bowel function (such as passage of flatus) occur.

Comparisons between pre- and postambulatory recordings for group A patients were made using paired Student's t test. Comparisons between group A (preambulatory) and group C studies were made using unpaired Student's t test. Comparison between group A (preambulatory) and group C studies to determine if increased numbers of patients demonstrated spike activity after ambulation was done with a chi square test and the Yates correction where necessary because of expected frequencies less than 20. Data are expressed as mean ± standard error of the mean.

Results

Slow Waves

Gastric fundus and body slow waves were seen clearly as early as 12 hours after operation and then daily during each recording session in all group A patients. There were no significant differences in the gastric body or fundus slow wave frequencies in the first week after operation between the pre- and postambulation recordings. Neither was there a difference in fundus and body slow waves between the daily group A preambulation frequency and the group C frequency (Table 1). There was a difference between group A and group C gastric body frequencies at 1 month (group A, 2.86 ± 0.07; group C, 3.17 ± 0.11; $p < 0.025$).

Slow waves from the small intestine were present on the first postoperative recordings in all patients in groups A and C. Slow waves were noted in the Roux limb and jejunum distal to the enteroenterostomy and were no different in frequency from those seen in the jejunum in continuity with the duodenal pacemaker. Ambulation in group A patients did not have any effect on slow wave frequency during the first postoperative week in any of the jejunal segments recorded (Table 2). There was also no difference in frequency between group A preambulation frequency and group C frequency during this time period or 1 month after surgery.

The colon had the most complex slow wave patterns of the three intestinal areas studied. Three different and distinct slow wave frequencies were recorded from the

TABLE 2. *Small Bowel Slow Waves (per minute)*

Day	1–2	3–4	5–7	1 month
Preambulation				
Roux	11.20 ± 0.14	10.98 ± 0.18	10.57 ± 0.16	11.20 ± 0.18
J_1J_2	11.15 ± 0.13	11.12 ± 0.14	10.78 ± 0.14	11.04 ± 0.16
J_3J_4	11.33 ± 0.15	10.84 ± 0.14	10.70 ± 0.15	10.95 ± 0.28
Postambulation				
Roux	11.35 ± 0.15	10.88 ± 0.20	10.49 ± 0.18	—
J_1J_2	11.33 ± 0.19	10.94 ± 0.16	10.82 ± 0.17	—
J_3J_4	11.31 ± 0.17	10.92 ± 0.19	10.80 ± 0.24	—
Control				
Roux	11.14 ± 0.25	10.89 ± 0.23	10.85 ± 0.15	10.81 ± 0.15
J_1J_2	11.33 ± 0.19	11.24 ± 0.20	10.96 ± 0.14	10.92 ± 0.21
J_3J_4	10.77 ± 0.20	10.69 ± 0.27	10.56 ± 0.15	10.53 ± 0.19

—, Results not applicable at 1 month.

mid transverse colon electrodes. Clearly there was a low frequency range of approximately 2 to 4 cycles per minute (cpm), a mid frequency range of 9 to 11 cpm, and a high frequency range of 22 to 26 cpm. These patterns often were noted separately or superimposed on each other. Slow waves in all three frequency ranges were noted on the first postoperative day in various patients; however all three were not always present on individual patient recordings. During the first 1 to 2 days after operation, there tended to be a predominance of mid frequency range slow waves. By the third to fourth postoperative day, mid and high frequency range waves always were present in groups A and C, with the higher frequencies increasing in activity until the colon resembled a more normal myoelectric pattern with the presence of continuous electric-response activity. Generally this occurred around the fifth postoperative day. The one exception was a woman in group A who developed bowel ischemia and only had mid frequency range waves during her study. Colon low frequency range slow waves were not always discernible on all recordings.

No difference was noted for low, mid, or high range colon slow wave frequencies between group A preambulation and postambulation recordings at any time during the first postoperative week. Group A preambulation frequencies in all three ranges also were not different from those noted in group C during the first week or 1 month after surgery (Table 3).

Spike Activity

The presence and percentage of spike potentials associated with gastric slow waves was very variable in both the ambulatory and control groups. Spike activity was present in the fundus in 14 of 29 group A recordings and 8 of 32 group C recordings, but in too few patients and with insufficient activity (much less than 10% of slow waves) during each data collection period for meaningful statistical analysis.

TABLE 3. *Transverse Colon Slow Waves (per minute)*

Frequency Range	1–4 Days	5–7 Days	1 Month
Preambulation			
Low	2.80 ± 0.14	3.00 ± 0.0	3.25 ± 0.18
Mid	11.36 ± 0.32	10.98 ± 0.40	10.25 ± 0.41
High	24.17 ± 0.84	23.33 ± 0.89	24.67 ± 0.36
Postambulation			
Low	2.96 ± 0.13	2.75 ± 0.18	—
Mid	11.26 ± 0.24	10.86 ± 0.29	—
High	23.50 ± 0.90	23.67 ± 1.11	—
Control			
Low	2.78 ± 0.10	2.77 ± 0.14	2.85 ± 0.25
Mid	11.23 ± 0.90	10.33 ± 0.27	11.07 ± 0.60
High	25.29 ± 1.21	23.42 ± 1.71	21.25 ± 1.30

—, Results not applicable at 1 month.

Spike activity was recorded more frequently from the gastric body in 32 of 52 group C recordings and 33 of 48 group A recordings during the 1-month study period. Phase III-like activity was present in 7 group C and 12 group A preambulation gastric body recordings, with 100% slow waves associated with spike potentials for 2 to 3 minutes. These periods of activity were not associated with a preceding phase II type of activity, as is seen in the small bowel. Non-phase III type spike activity ranged from 2% to 66% activity. Approximately 50% of the time there were less than 10% slow waves with associated spike potentials. Activity with more than 10% spike potentials occurred at the most on three recordings in any data collection period and often occurred only once. These areas of activity were limited to recording segments of 5 minutes or less. Generally there was absence of spike activity, as is seen in phase I of the small intestine.

There was no difference in percentage of phase III or non-phase III activity between the group A pre- and postambulation recordings or the group A preambulation and group C recordings during the first postoperative week. There also was no difference in group A preambulation and group C spike activity at 1 month (Table 4). Data also were analyzed for the number of recordings demonstrating non-phase III and for those demonstrating phase III spike activity, as noted in Table 4. There was no change in the number of recordings with either type of spike activity between group A pre- and postambulation or group A preambulation and group C patients during any recording interval, although, as noted, there were 71% more MMCs throughout the entire study in group A preambulation studies than in group C (12 *versus* 7).

Small Bowel

Phase II and phase III spike activity was noted on postoperative day 1 and throughout the study in all small intestinal segments. There was no difference in percentage of slow waves with associated phase II or phase III spike activity at the J1J2 recording site between group A pre- and postambulation or group A preambulation and group C studies at any time (Table 5). No difference in phase II or III spike activity was noted in the Roux (R1R2) or J3J4 leads between group A pre- and postambulation throughout the study. Both the Roux limb and J3J4 leads recorded increased phase II activity on postoperative days 1 and 2 in the group A preambulation recordings compared to group C recordings (Roux: group A, 75% ± 10%; group C, 47% ± 6%; $p < 0.025$) (J3J4: group A, 70% ± 5%; group C, 57% ± 5%; $p < 0.05$). There were no significant differences at any other time during the first week or at 1 month. No differences in phase III activity were found in

TABLE 4. *Gastric Body Spike Potentials (in %)*

	1–2 Days	3–4 Days	5–7 Days	1 Month
Preambulation				
Non PIII	14.3 ± 4.2 (3/14)*	16.6 ± 11.1 (5/13)	23.6 ± 7.6 (5/11)	24.7 ± 4.7 (3/6)
PIII	100.0 ± 0.0 (5/14)	100.0 ± 0.0 (3/13)	100.0 ± 0.0 (3/11)	100.0 ± 0.0 (1/6)
Postambulation				
Non PIII	10.3 ± 3.6 (3/10)	24.2 ± 9.6 (5/12)	13.5 ± 6.2 (4/10)	—
PIII	100.0 ± 0.0 (4/10)	100.0 ± 0.0 (4/12)	100.0 ± 0.0 (3/10)	—
Control				
Non PIII	11.6 ± 8.6 (5/13)	16.6 ± 8.8 (9/15)	32.2 ± 10.2 (8/13)	48.0 ± 13.6 (3/6)
PIII	100.0 ± 0.0 (2/13)	100.0 ± 0.0 (2/15)	100.0 ± 0.0 (3/13)	not present

* Patients with spike potentials/total patients.

—, Results not applicable at 1 month.

the Roux or J3J4 leads between group A preambulation and group C patients.

Colon

Discrete electric-response activity (DERA) was noted to return as early as postoperative day 1 in some recordings in both groups A and C. Continuous electric-response activity (CERA) returned no earlier than postoperative day 2 but was, on average, not present until the fifth day. Ambulation was not found to cause an early return of either DERA or CERA when comparing group A preambulation results to group C results (Table 6). No difference was noted in the time of return of either type of activity between group A pre- and postambulation recordings.

Clinical recovery of gastrointestinal functions evidenced by passage of flatus and stool was not affected by ambulation. Group A had return of normal bowel function on day 5.1 ± 0.6, while group C had return on day 5.2 ± 0.4 (Table 6).

Discussion

Although controversial in the past, ambulation in those who are able is now a routine aspect of postsurgical care. The long-held belief that wounds require prolonged immobilization to properly heal has been dispelled, as has the erroneous belief that early ambulation would increase the danger of deep venous thrombosis and pulmonary embolism. In fact the opposite is true. McDowell reported a case of early ambulation in 1817, but the patient's early departure from bed was regarded as an act of foolishness.[1] The earliest known advocate for early postoperative ambulation in the surgical literature was Dr. Emil Ries of Chicago in 1899.[5] Most of his colleagues disagreed, however, including Dr. William S. Halsted, who kept his hernia patients in bed for 21 days. While physicians in Europe, Africa, and South America adopted early ambulation, the practice did not become commonplace in the United States until the 1940s. Daniel J. Leithauser had much to do with the rebirth and acceptance of early ambulation in United States hospitals.[2,3] Articles by Ochsner and DeBakey[6] and by Schafer and Dragstedt[7] soon followed, and by 1950 early ambulation was an established practice.

Research concerning the beneficial effects of early ambulation is fairly extensive. Studies have been conducted concerning the effects of ambulation on thromboembolism, pulmonary complications, and results following various orthopedic procedures and cardiac operations.[8,9] Not all areas concerning early ambulation have been well researched, however, and there are still some areas for which anecdotal or personal experience are the basis for common belief. Frequently patients are encouraged to ambulate postoperatively with the belief that this will improve bowel function and help dispel the cramps and bloating that often accompany gastrointestinal recovery from ileus. However, to our knowledge, no measurement of physiologic parameters to confirm this purported beneficial effect of early postoperative ambulation on gastrointestinal function has been done.

Data from this study indicate that the recovery of nor-

TABLE 5. *Small Bowel Spike Potentials—Phase II (in %)*

	1–2 Days	3–4 Days	5–7 Days	1 Month
Preambulation				
Roux	75 ± 10*	74 ± 10	63 ± 19	59 ± 7
J_1J_2	53 ± 4	62 ± 5	63 ± 7	58 ± 4
J_3J_4	70 ± 5†	69 ± 3	57 ± 6	60 ± 4
Postambulation				
Roux	76 ± 7	80 ± 4	33 ± 13	—
J_1J_2	59 ± 9	61 ± 8	62 ± 12	—
J_3J_4	88 ± 8	71 ± 6	35 ± 10	—
Control				
Roux	47 ± 6	73 ± 7	54 ± 5	59 ± 6
J_1J_2	45 ± 6	65 ± 10	55 ± 5	51 ± 7
J_3J_4	57 ± 5	58 ± 7	51 ± 8	59 ± 7

* $p < 0.025$ compared to control group.

† $p < 0.05$ compared to control group.

—, Results not applicable at 1 month.

TABLE 6. *Transverse Colon—Return of Spike Activity/Clinical Recovery (in days)*

Group	DERA	CERA	Clinical
Group A	2.0 ± 0.4	5.1 ± 0.6	5.1 ± 0.6
Group C	2.1 ± 0.4	6.0 ± 0.7	5.2 ± 0.4

DERA, discrete electric-response activity.
CERA, continuous electric-response activity.

mal fasting gastrointestinal myoelectric activity patterns are not expedited by early postoperative ambulation, at least not by the extent to which our patients ambulated. Slow waves from the gastric fundus, body, and the jejunum were present by postoperative day 1 and not surprisingly, their frequency was never altered by ambulation. The only difference noted for any of the group comparisons for gastric and small intestinal slow wave activity was a lower slow wave frequency in the gastric body at 1 month when comparing control and early ambulation patients. The patients were not ambulated during the recording study at this point and it is unlikely that ambulation in the early postoperative period accounts for this difference. Neither frequency can be regarded as abnormal and there was no tachygastria or other dysrhythmia. Clinically there was no apparent difference in the gastric function of these patients 1 month after surgery.

Colonic slow waves were more complex than those in the other two areas of the alimentary tract. Generally two different slow wave frequencies have been described in the human colon: a low frequency range of approximately 2 to 5 cpm or 2 to 9 cpm and a higher frequency range of 6 to 10 cpm or 9 to 13 cpm, depending, in part, on the author or section of colon studied.[10–12] Huizinga[13] describes spontaneous electric oscillatory activity with frequencies ranging from 4 to 28 cpm in the circular muscular layer of the human colon. Our data showed three distinct slow wave patterns in the mid-transverse colon: a low frequency range of 2 to 4 cpm, a mid range of 9 to 11 cpm, and a high frequency range of 22 to 26 cpm. There were few tracings that showed slow waves with frequencies outside of these ranges. All three frequency ranges were noted in various recordings on the first postoperative day, although the high frequency ranges were not prominent until the third to fourth postoperative day. One-month postoperative recordings showed an equal predominance of mid and high frequency range activity superimposed on the low frequency range activity. Recovery of this pattern was not enhanced by ambulation to the extent that it was performed in these studies.

Spike activity in the gastric body and fundus was noted as early as postoperative day 1, although fundic spike activity occurred very infrequently throughout the study. Gastric body non-phase III spike activity, while more frequent than in the fundus, was still somewhat variable in its presence or absence. Although not examined in this study, we examined the antrum in other protocols and found the amount of spike activity there to be higher and more consistent. These findings correlate well with the observed physiology of the stomach where the fundus acts as an expandable reservoir with little contractile activity and the antrum is involved with grinding of solid foods. There was no evidence that ambulation increased the percentage of slow waves associated with phase III and nonphase III activity during any of the recording periods.

Phase II and phase III spike activity from the jejunum in continuity with the duodenal pacemaker was not affected by ambulation acutely or overall. Phase II activity in the Roux limb and at the J3J4 leads was increased compared to controls on day 1 to 2 but was the same thereafter. It may be that severance from the pacemaker caused a transient alteration in the myoelectric activity, although it was noted that the Roux and J3J4 slow waves were no different from controls during that period. By the third and fourth postoperative days and at 1 month, spike activity was essentially the same in all small bowel segments. The early differences appeared to have no clinical significance.

The colon showed normal or recovered myoelectric patterns approximately 5 days after operation that were the same as tracings obtained 1 month after surgery. Return of clinical colon function with passage of flatus and stool correlated well with the return of normal colon myoelectric patterns. This suggests that myoelectric activity in the colon closely follows function and is a good parameter for the study of colon function. As would be expected from the myoelectric findings, ambulation did not enhance the clinical return of colonic bowel function either.

Ambulation appears to have no overall effect on promoting an early recovery of normal gastrointestinal myoelectric activity. These results are contrary to our hypothesis before the study. The lack of evidence to support the contention that ambulation, at least ambulation to the degree that group A patients walked, is beneficial for recovery of gut function after surgery does not suggest that the practice of early postoperative ambulation should be discontinued. We would, in fact, encourage its use because it probably does have beneficial effects in preventing postoperative problems related to deep venous thrombosis, muscle atrophy, and protein use. These and other psychologic benefits of early ambulation are important in enhancing recovery after surgery. We advocate continued early ambulation following laparotomy but our attempts to improve resolution of postoperative ileus with ambulation must be tempered, however, with the knowledge that the results may be more perceived than real.

Acknowledgments

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Efficacy of Octreotide Acetate in Treatment of Severe Postgastrectomy Dumping Syndrome

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The present study evaluates the acute and chronic use of a long-acting somatostatin analog, octreotide acetate, in the treatment of patients with severe postgastrectomy dumping syndrome. In the acute phase, 10 patients with severe dumping were studied over 2 consecutive days before and for 3 hours after the ingestion of a 'dumping breakfast' in a randomized double-blind fashion. On one day octreotide (100 μg) was given subcutaneously 30 minutes before the test meal and on the other day an equal volume of vehicle was injected. An additional group of six postgastrectomy patients without dumping were studied in a similar fashion and these acted as controls. During placebo treatment the test meal resulted in an immediate increase ($p < 0.01$) in the pulse rate and in plasma levels of glucose, glucagon, pancreatic polypeptide, neurotensin, and insulin. Similar changes were seen in the control group with respect to placebo; however glucagon and neurotensin ($p < 0.05$) did not show the same magnitude of increase as seen with placebo. Treatment with octreotide acetate prevented the development of both vasomotor and gastrointestinal symptoms and completely ablated all of the above responses in plasma peptides. These changes were associated with complete ablation of diarrhea ($p < 0.001$). Pretreatment with octreotide acetate completely suppressed the rise in plasma insulin response to the meal and this ablated the late hypoglycemia of dumping. Treatment with octreotide acetate resulted in delayed gastric emptying and transit time (578 ± 244 minutes) *versus* 76 ± 23 minutes with placebo and 125 ± 36 minutes in controls ($p < 0.05$). Chronic daily treatment with octreotide acetate resulted in minimal side effects. These patients demonstrated a stable fasting plasma glucose, normal liver function tests, and an average weight gain of 11% during a 12-month period. In addition most patients were able to resume employment. The long-acting somatostatin analog, octreotide acetate, is highly effective in preventing the development of symptoms of severe dumping syndrome, both vasomotor and gastrointestinal.

THE DUMPING SYNDROME, DESCRIBED by Mix in 1922,[1] results from the alteration, ablation, or bypass of the pyloric sphincter mechanism. Nearly one half of all patients who undergo gastric operations develop symptoms of dumping but less than 5% of these patients have severe symptoms requiring other forms of treatment after dietary management has failed.[2] Early dumping symptoms typically are observed within 15 to 30 minutes after the ingestion of a high carbohydrate meal. The syndrome is characterized by sudden onset of vasomotor symptoms, such as diaphoresis, palpitations, weakness, faintness, and an intense desire to lie down. The gastrointestinal symptoms are more distressing with abdominal bloating, cramping, and profound diarrhea usually within 1 hour after a meal. Late dumping symptoms occur much less frequently than early dumping but can occur in combination with early dumping. These symptoms, including perspiration, rapid heart rate, mental confusion, and syncope occur 1 to 2 hours after a meal and are thought to be the result of insulin-induced hypoglycemia.

The range of symptoms in patients with dumping syndrome vary widely from minimal symptoms only with certain foods to profound dumping with almost all foods. Severe symptoms result in marked weight loss, fear of eating, fear of leaving the house, and, in most cases, the inability to work full-time.[3] Patients with severe dumping

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have been associated with a significant psychologic overlay[4] causing a magnification of symptoms. However these patients are now being recognized as having other physiologic reasons for the symptoms of the dumping syndrome.[5–9]

The exact etiology of dumping is unknown. The release of several humoral agents is increased in patients with dumping and not in asymptomatic postgastrectomy patients, thus implicating them in the pathogenesis of the syndrome. The agents include glucagon, neurotensin,[5] vasoactive intestinal peptide,[6] serotonin,[7] and bradykinin.[8] We and others[10–12] hypothesized that if these factors or hormones could be inhibited with somatostatin it might be possible to ablate the symptoms of dumping. Octreotide acetate (Sandostatin, Sandoz, East Hanover, NJ), is a somatostatin analogue that has a longer half-life, which allows administration *via* a subcutaneous route. In the present study, octreotide acetate was evaluated in an acute double-blind randomized prospective trial in alleviating the symptoms associated with severe dumping syndrome. This study also examines the efficacy of chronic treatment (up to 15 months) of patients with severe dumping syndrome.

Materials and Methods

Patients with severe dumping syndrome were selected by a careful history of their symptom complex. Selection included failure of dietary manipulation, weight loss of more than 10% of body weight, and symptoms causing a significant alteration in lifestyle. The symptoms included faintness, weakness, diaphoresis, palpitations, abdominal bloating, cramping, nausea, and diarrhea (more than 5 episodes per day). The selection process also included reproducing the symptoms after the ingestion of a solid 'dumping breakfast'; this consisted of a 750-kcal solid meal with 21 g protein, 30 g fat, and 99 g carbohydrate. At the end of this trial, the patients were asked to rank their symptoms on a severity scale from 0 (no symptoms) to 10 (the most severe symptoms). The efficacy of this scale was tested repeatedly (on 3 to 7 occasions) for each subject, with an intraindividual variability of 2.5% ± 0.1%. Only patients with severity scores more than 7 following the 'dumping breakfast' trial were invited to participate in the present study. Eight patients had severe symptoms of early dumping with no late dumping and two patients had symptoms suggestive of both severe early and late dumping (Table 1). Six postgastrectomy patients with no symptoms of dumping also were studied to measure gastric emptying and hormonal response and served as controls.

All patients signed an informed consent form before entering the study. The protocol was approved by the Institutional Committee for the Protection of Human Subjects at Vanderbilt University. The patients were studied on two consecutive days in the Vanderbilt Clinical Research Center. Each patient was fasted overnight and then studied, before and for 3 hours after the ingestion of a high caloric 'dumping breakfast' meal. On one day, 100 μg of octreotide acetate was given subcutaneously 30 minutes before the test meal (denoted octreotide trial) and on the other day an equal volume of vehicle (denoted placebo trial) was injected. All patients were studied in the supine position. The order of the trials were assigned in a randomized double-blind fashion, both to the inves-

TABLE 1. *Patient Characteristics*

Patient	Age (years)	Sex	Operative Procedure	Duration of Symptoms (years)	Percentage of Body Weight Loss	Type of Dumping
1	34	M	Total gastrectomy	12	25	Early + late
2	60	F	Vagotomy and antrectomy + Billroth I	4	16	Early
3	50	F	Vagotomy and antrectomy + Billroth I	1	15	Early
4	35	F	Vagotomy and antrectomy + Roux-en-Y	8	50	Early + late
5	62	F	Vagotomy and antrectomy + Billroth I	2	24	Early
6	46	M	Vagotomy and antrectomy + Billroth I	7	44	Early
7	33	F	Vagotomy and antrectomy + Billroth I	4	43	Early
8	70	M	Vagotomy and antrectomy + Billroth II	34	10	Early
9	41	M	Vagotomy and antrectomy + Roux-en-Y	3	33	Early
10	61	F	Vagotomy and antrectomy + Billroth I	14	25	Early

M, male; F, female.

tigator and the patient. Blood samples were obtained from an indwelling intravenous catheter every 15 to 30 minutes during the study period for the determination of plasma glucose and intestinal peptides. Blood pressure and pulse rate were monitored continuously throughout the study period. At the conclusion of the study the patients were asked to rank their symptoms again.

At the end of the second study day, the blinding code was broken and the patients were informed of the outcome. All patients were placed on chronic maintenance therapy with the somatostatin analogue, with doses varying from 30 to 70 µg subcutaneously taken three to four times each day. On three occasions the analog was given 30 minutes before each meal and also was given at bedtime.

Analysis of plasma glucose was performed using the glucose oxidase method. Plasma concentrations of vasoactive intestinal peptide,[13] pancreatic polypeptide,[13] motilin,[14] insulin,[15] glucagon,[16] and gastrin[17] were measured using established radioimmunoassay methods. Plasma concentrations of neurotensin were determined in unextracted plasma by a modification of a previously described assay.[18] All plasma samples for measurement of a given peptide were tested in a single assay; the intra-assay coefficient of variation was less than 6% for all assays.

Gastric emptying was assessed in five dumping and five control patients using standard solid-phase Technetium^{99}-labeled scrambled eggs as the test meal. Gastric emptying was quantitated as the time it took for one half of the radiolabel to leave the stomach. The normal $T_{1/2}$ of gastric emptying is 60 to 90 minutes.

Results are expressed as the mean ± standard error of the mean (SEM). Statistical analysis was performed using Student's paired t test and analysis of variance, where applicable.

Results

Patient Characteristics (Table 1)

Ten patients (four men and six women) were included in the study. The mean age was 49 years (range, 33 to 70 years). All patients had previous gastric surgery. Vagotomy and antrectomy was performed in nine of the patients; six had Billroth I anastomosis, one had a Billroth II anastomosis, and two had Roux-en-Y-gastrojejunostomies. One patient had a total gastrectomy. All manifested dumping symptoms that have lasted from 1 to 34 years, with a mean of 8.9 years. Nine of the ten patients had significant weight loss (15% or more) since the onset of dumping symptoms. In the control group, six patients (three men and three women) were studied. Mean age was 54 years (range, 53 to 69 years). All had previous gastric surgery. Vagotomy and antrectomy was performed in five patients; three had Roux-en-Y-gastrojejunostomies, one had a Billroth I, and one had a Billroth II reconstruction. One patient had a total gastrectomy. No dumping symptoms were present in any of these postgastrectomy patients.

Pulse Rate and Blood Pressure (Fig. 1)

A significant increase in pulse rate was seen during the placebo trial within 15 minutes of meal consumption ($p < 0.01$). This effect persisted until the end of the 3-hour experimental period when the pulse rate returned to basal levels. Octreotide acetate completely ablated the increase in pulse rate. Neither trial showed any significant change in the systolic, diastolic, or mean arterial blood pressures after the test meal (data not shown).

Dumping Symptoms (Fig. 2)

The severity score of dumping symptoms during the placebo trial was 8.5 ± 0.5. When octreotide acetate was given before the meal, we observed a marked reduction in the symptom severity score to 1.7 ± 0.5 ($p < 0.001$). Within 3 hours of meal ingestion, 8 of the 10 patients receiving the placebo trial developed severe diarrhea, with a frequency of 1.7 episodes (range, 2 to 5 episodes). None of the patients treated with octreotide acetate developed diarrhea ($p < 0.001$). In the two patients with late dumping, their symptoms were completely ablated with octreotide acetate treatment. The only adverse effects of octreotide was mild transient (lasting an average of 5 minutes) abdominal cramping noted in four patients, which occurred shortly after injection of the drug.

Plasma Glucose Levels (Fig. 3)

Basal plasma glucose levels were identical in the dumping and nondumping postgastrectomy subjects and averaged 86 ± 2 mg/dL. During the placebo trial, plasma glucose rose to peak levels of 190 ± 18 mg/dL within 45 minutes and returned to basal levels by 120 minutes. The increase in plasma glucose in the octreotide trial was much greater ($p < 0.01$), reaching peak levels of 277 ± 25 mg/dL by 75 minutes and decreased to 183 ± 14 mg/dL by the end of the experimental period. The two patients with late dumping symptoms manifested profound hypoglycemia, with an average nadir plasma glucose level (44 mg/dL) at 90 minutes; this was ablated with pretreatment with octreotide acetate.

Plasma Insulin and Glucagon Levels

During the placebo trial plasma insulin levels increased to peak levels 10 to 12 times basal in response to the meal, as shown in Figure 4; the peak levels coincided with those of plasma glucose. The increase in plasma insulin was completely blocked by octreotide acetate pretreatment (p

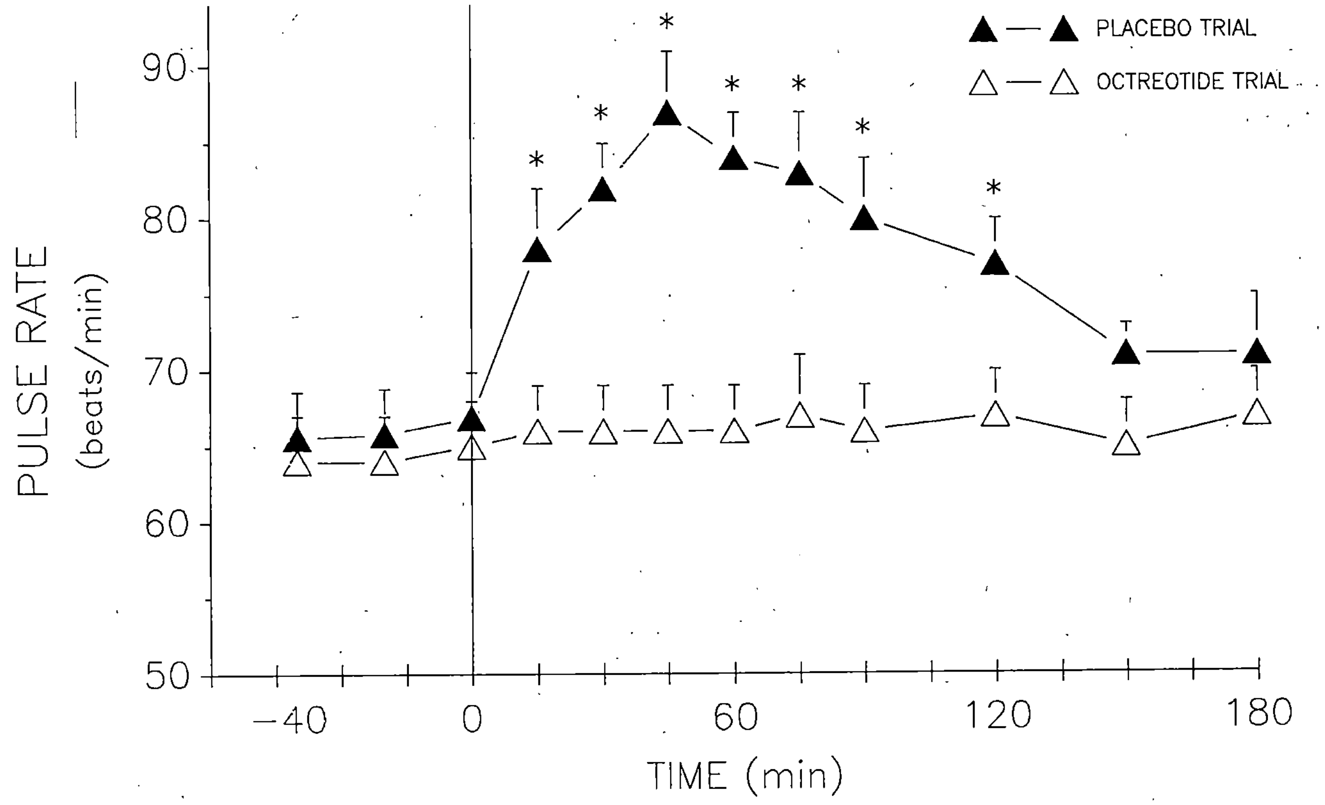


FIG. 1. Pulse rate (beats/minute) in 10 subjects known to have severe dumping symptoms, before and after a high carbohydrate breakfast given at 0 minutes and consumed within 15 minutes. Thirty minutes before the meal, the patients received a subcutaneous injection of 100 μg of octreotide acetate (open triangles), or a vehicle (closed triangles). (* Denotes differences between the group at $p < 0.01$.)

< 0.01). Changes in plasma glucagon paralleled those of insulin and, as shown in Figure 5, were inhibited by octreotide acetate treatment. The control group showed a similar increase in plasma insulin as the patients while receiving the placebo trial. In addition they manifested a very slight rise in plasma glucagon but not to the same magnitude as that seen in the patients during the placebo trial ($p < 0.05$).

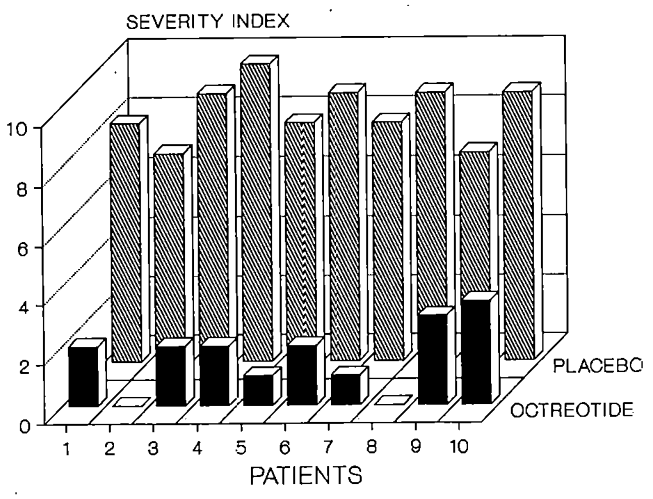


FIG. 2. Severity score for dumping symptoms of each of the 10 patients described in Figure 1, treated with octreotide (closed bars) or placebo (hatched bars). A score of zero denotes no symptoms and a score of 10 denotes severe symptoms.

Intestinal Peptides

Plasma levels of the octreotide acetate reached peak values of 4698 ± 821 pg/mL within 10 minutes of a subcutaneous injection of 100 μg, as shown in Figure 6. Subsequently the decrease in plasma levels of the drug followed a first-order kinetics with drug levels still exceeding 1000 pg/mL at the end of the 3-hour study period. The half-life of the drug calculated from Figure 6 was 90 minutes.

Five intestinal peptides were measured in this study: gastrin, neurotensin, motilin, pancreatic polypeptide, and vasoactive intestinal peptide (VIP). The levels of neurotensin and pancreatic polypeptide were significantly elevated during the placebo trial, as shown in Figure 7. The increase in both peptides, however, was abolished during the octreotide trial groups ($p < 0.05$). Following the breakfast meal, the subjects in the control group showed significant increases in the plasma levels of neurotensin and pancreatic polypeptide. The increase in neurotensin was blunted when compared to the levels seen in the

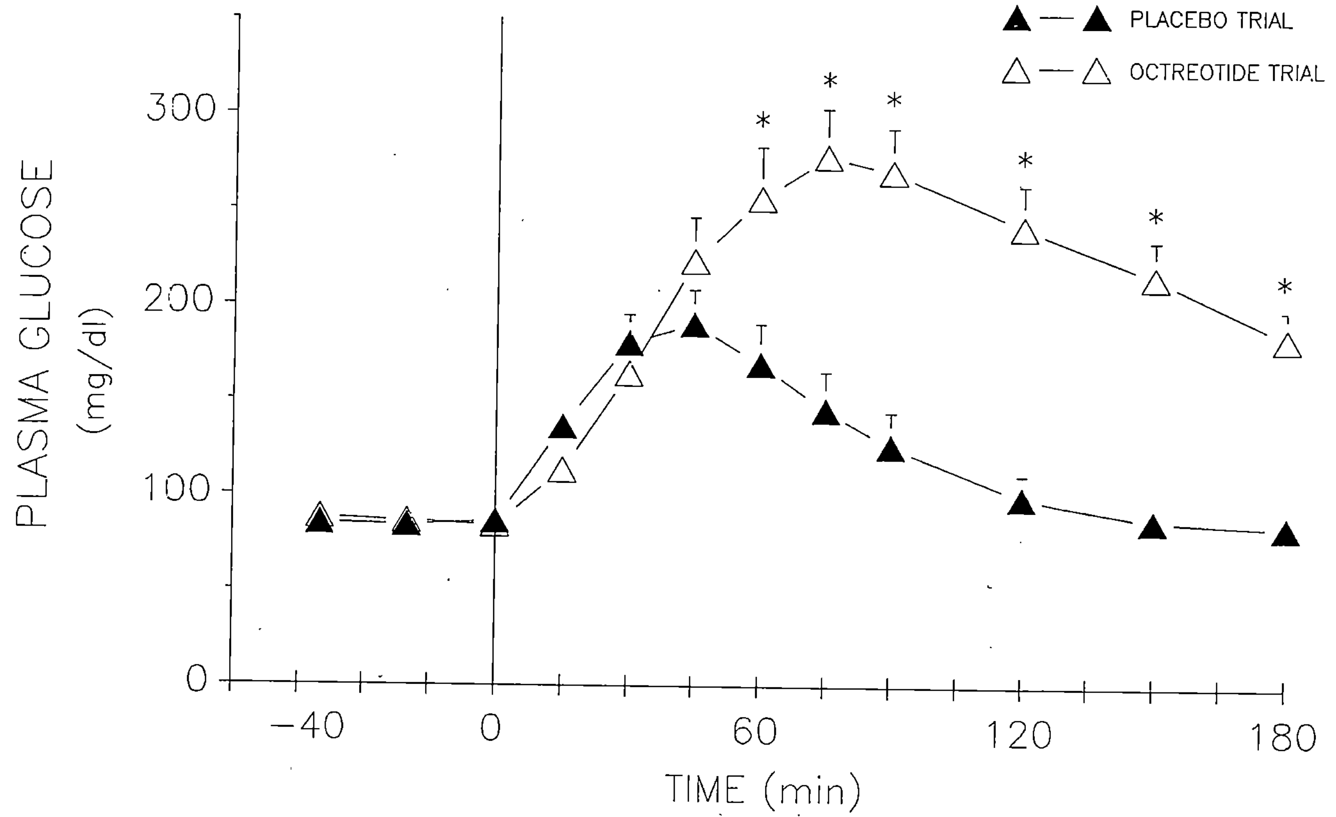


FIG. 3. Plasma glucose concentrations after a high carbohydrate meal in patients pretreated with (open trianlges) octreotide or with placebo (closed triangles). The patients were described in Figure 1. (* Denotes difference between groups at $p < 0.01$.)

dumping patients during placebo trial and were significantly higher than those seen in the patients during the octreotide trial. Plasma levels of gastrin, motilin, and vasoactive intestinal peptide showed no significant changes in any of the groups (data not shown) in response to the meal.

Gastric Emptying (Table 2)

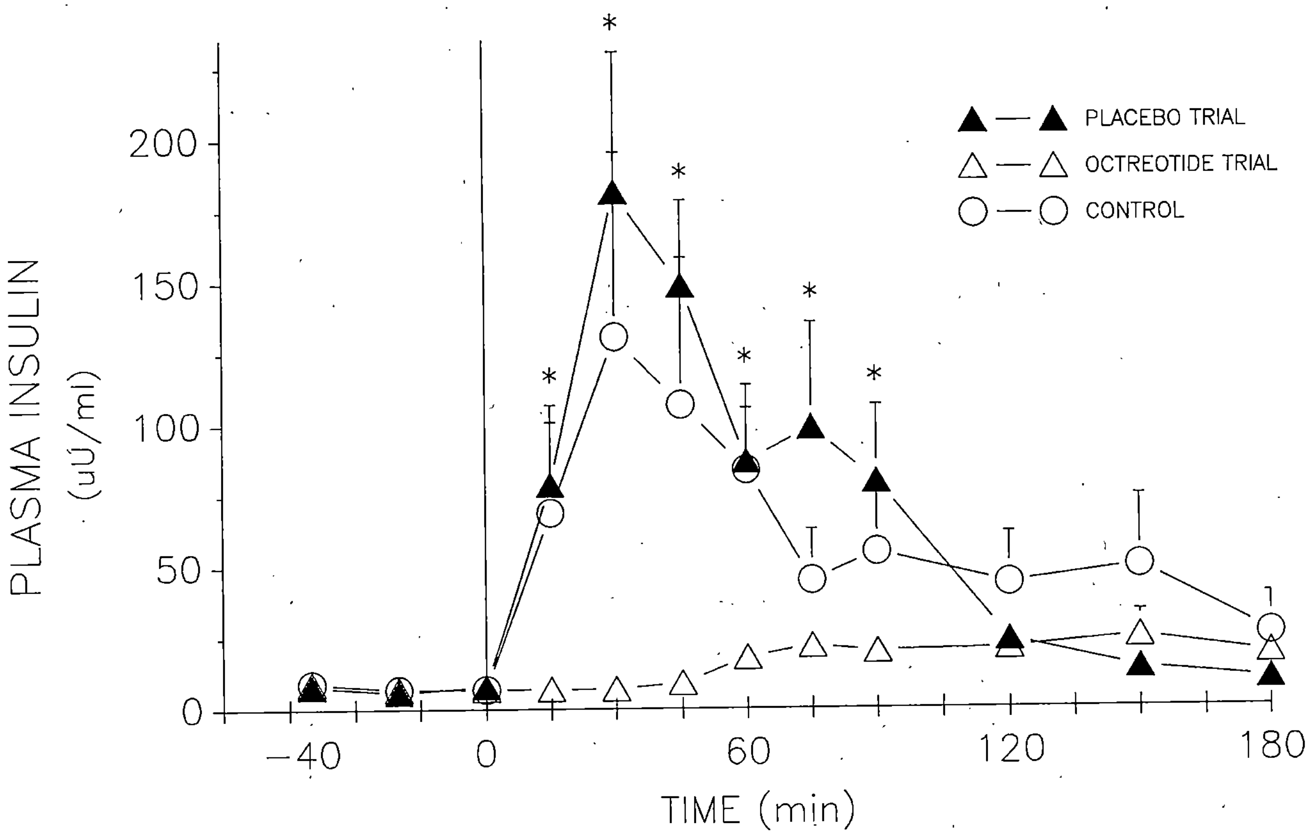
Gastric emptying was assessed by Technetium^{99}-labeled scrambled eggs in five patients with and without treatment with octreotide. The mean emptying time during the placebo trial averaged 76 ± 23 minutes, with a wide range of variability (21 to 150 minutes). These values were not significantly different from those seen in the nondumping patients or from normal controls (125 ± 32 minutes). This is attributed to the fact that the radiolabeled scrambled egg meal given did not contain high amounts of carbohydrates. Interestingly, in three subjects (3, 4, and 5) who manifested normal pretreatment retention times, emptying of gastric contents was associated with significant rush of food through the upper gastrointestinal tract, which was followed by diarrhea. In each of the patients studied, pretreatment with octreotide acetate prolonged the gastric emptying time ($p < 0.05$).

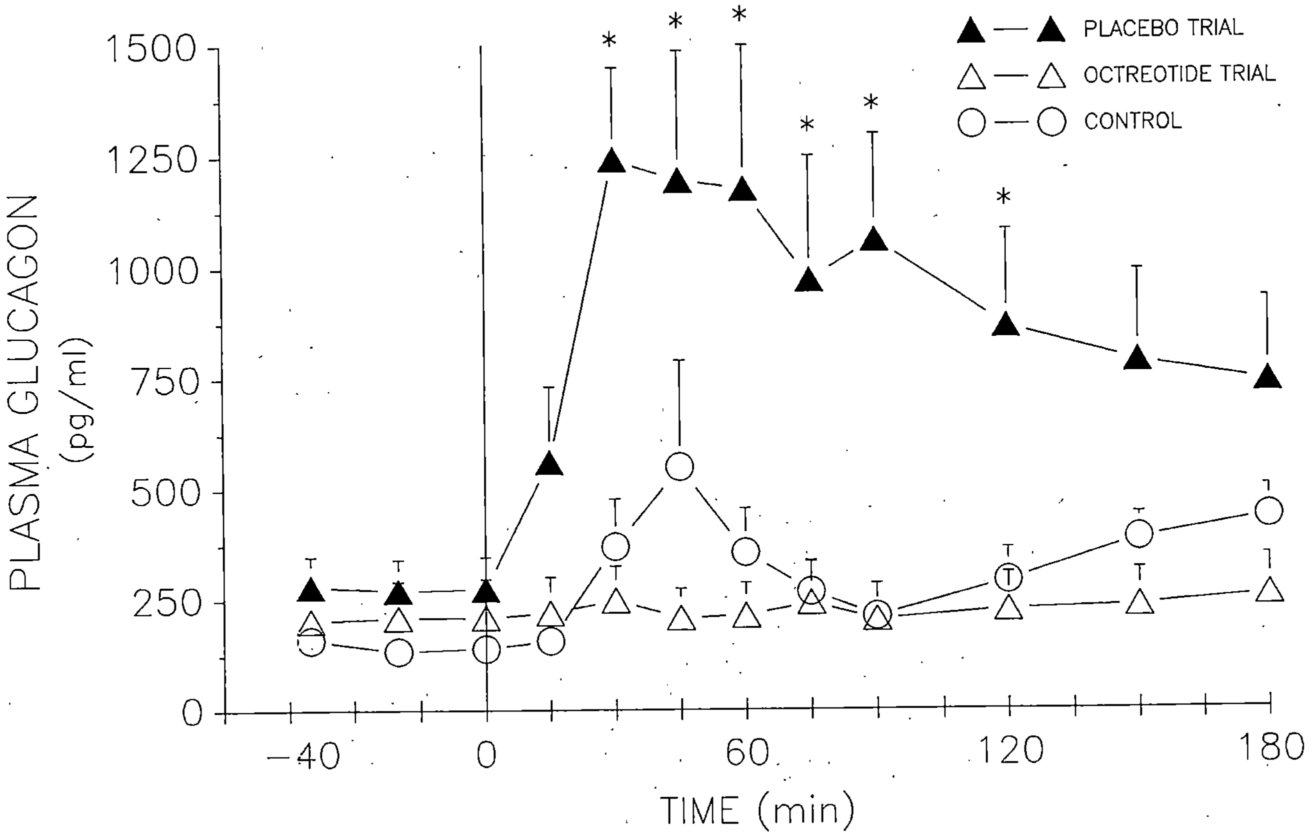
Long-term Studies

As already noted acute treatment with octreotide acetate resulted in a significant postprandial increase in plasma glucose levels and a blunted response in plasma insulin. These findings prompted us to investigate the long-term sequelae of octreotide acetate and particularly whether the long-term use of this drug is associated with a diabetic-like state. The subjects were followed monthly and biochemical parameters obtained at 3 and 15 months are shown in Table 3. Long-term treatment with octreotide acetate was associated with stablef fasting plasma glucose levels, normal liver enzymes, and a significant weight gain. Since beginning chronic treatment with octreotide acetate,

FIG. 4. (Top) Plasma insulin levels for the same patients described in Figure 1 while pretreated with octreotdie (open triangles) or with placebo (closed triangles). (* Denotes difference between ▲ and △, $p < 0.01$.)

FIG. 5. (Bottom) Plasma glucagon levels for the same patients described in Figure 1 with octreotide pretreatment (open triangles) or with placebo (closed triangles). (* Denotes difference between ▲ and △, $p < 0.01$ and ▲ and O, $p < 0.05$.)


PLASMA INSULIN (uU/ml)
0
50
100
150
200
TIME (min)
−40
0
60
120
180
*
▲—▲ PLACEBO TRIAL
△—△ OCTREOTIDE TRIAL
○—○ CONTROL


PLASMA GLUCAGON (pg/ml)
0
250
500
750
1000
1250
1500
TIME (min)
−40
0
60
120
180
*
▲—▲ PLACEBO TRIAL
△—△ OCTREOTIDE TRIAL
○—○ CONTROL

seven patients who were unemployed because of symptoms before the study have returned to work.

Discussion

The results of this double-blind prospective study show conclusively that the somatostatin analogue, octreotide acetate, is effective in preventing early dumping symptoms after ingestion of a high carbohydrate meal and prevented the appearance of hypoglycemia, a characteristic sign of late dumping symptoms. The present study also shows conclusively that long-term treatment with octreotide acetate (up to 15 months) was safe and resulted in significant weight gain and improved symptomatology. The overall well-being of these patients improved drastically.

The etiology of dumping syndrome remains largely unknown. Several theories have been proposed, and the most popular is the hyperosmolar load theory.[19] This theory states that the loss of the pyloric sphincter results in enhanced gastric emptying with rapid delivery of the hyperosmolar meal into the small intestine. This, in turn, causes a marked shift of extracellular fluid into the lumen, resulting in hemoconcentration and presumably a mild shocklike state.[20] It is uncertain whether the development of symptoms, both vasomotor and gastrointestinal, in these patients was directly related to the shocklike state or was the result of increased release of humoral factors. Johnson et al.[9] suggested that a transfusible factor was responsible for the development of dumping symptoms. Since that time a number of other investigators have implicated a variety of gastrointestinal hormones as the etiologic agent(s) in the dumping syndrome. These developments have lead us and others[10-12] to postulate that the use of somatostatin, which inhibits hormonal secretion, can ablate dumping symptoms.

Somatostatin, first discovered in the hypothalamic tissues, and presently known to be produced in several other tissues, including the antral mucosa, duodenum, pancreas, and testes has been shown to be a very potent inhibitor of the release of many peptides, primarily those formed by the gastropancreatic tissues.[21] Administration of somatostatin for the treatment of the dumping syndrome has, however, encountered limited success.[10,11] This was mainly due to the short half-life (1 to 2 minutes) of the peptide, which necessitates a continuous intravenous infusion to maintain adequate drug levels in the blood. Octreotide acetate (Sandostatin, Sandoz, East Hanover, NJ), described in 1982, is an octapeptide analogue of cyclic somatostatin. The chief advantage of the analogue over the natural compound, cyclic somatostatin, resides in its

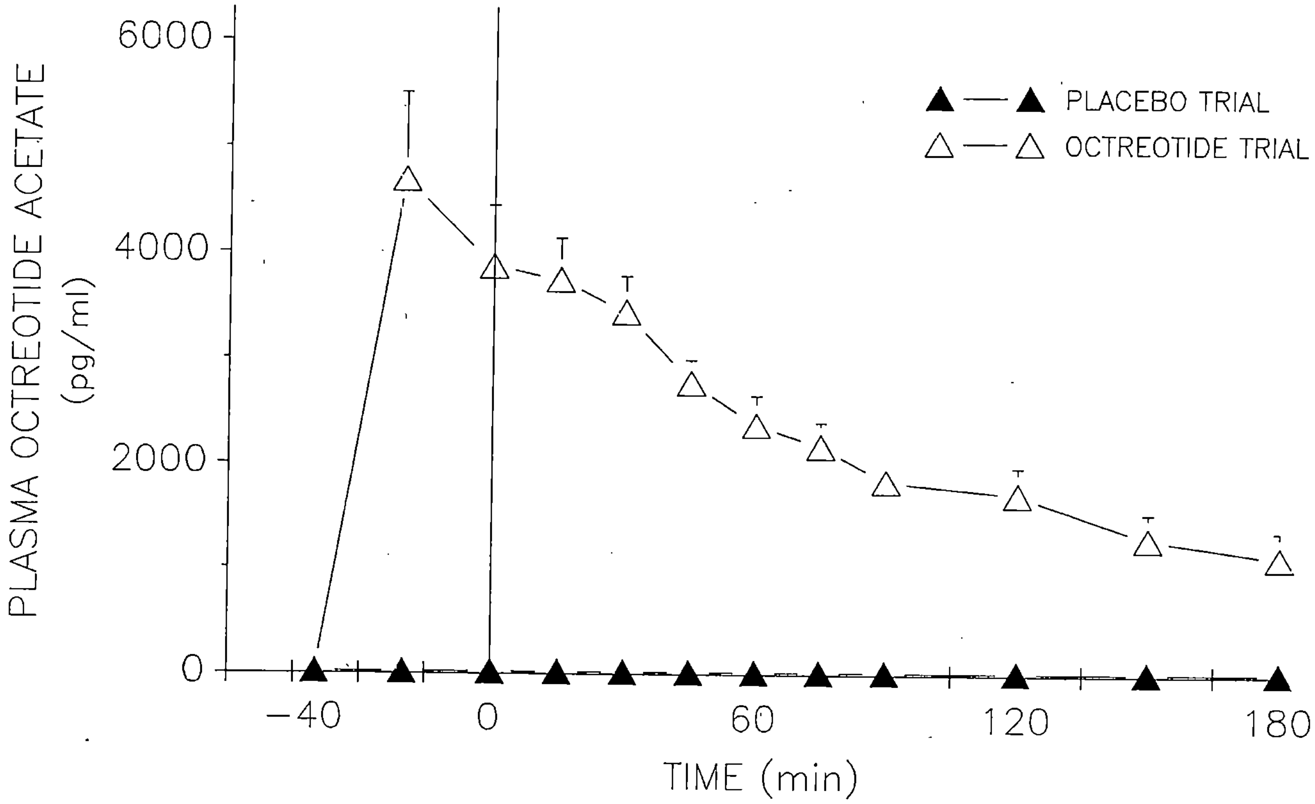


FIG. 6. Plasma levels of the somatostatin analogue in the subjects pretreated with octreotide and receiving a high carbohydrate meal, as described in Figure 1.

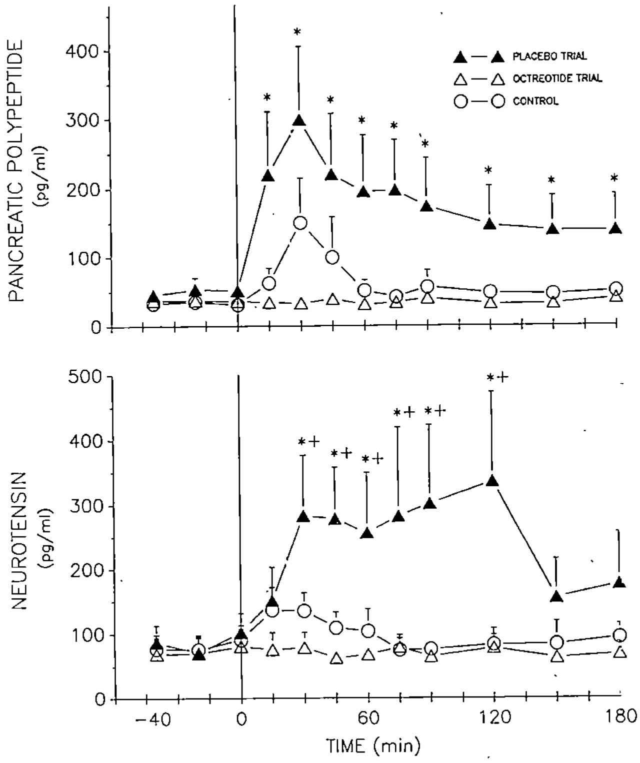


FIG. 7. Plasma levels of pancreatic polypeptide (upper panel) and neurotensin (lower panel) in the same subjects described in Figure 1 while pretreated with octreotide (open triangles) or placebo (closed triangles). (* Denotes difference between ▲ and △, $p < 0.01$ and + denotes difference between ▲ and △, $p < 0.05$.)

longer half-life (75 to 90 minutes *versus* 1 to 2 minutes), which allows its administration *via* a subcutaneous route. The biologic activity of this analogue is well maintained and compares well to that of cyclic somatostatin.[22] Octreotide acetate had been shown to be effective in a number of endocrine syndromes, including carcinoid,[23] insulinoma, VIPoma, and glucagonoma.[24]

TABLE 2. *Gastric Empying Time (t 1/2 in Minutes) in Postgastrectomy Subjects*

	Dumping		Nondumping
Patient	Placebo	Octreotide	Controls
3	150	1338	54
4	96	454	246
5	82	174	118
7	33	754	118
10	21	169	93
Mean ± SEM	76 ± 23	578 ± 244*	125 ± 36

The patients with dumping symptoms were studied twice, with and without pretreatment with octreotide acetate. The control subjects consisted of postgastrectomy patients who did not manifest any dumping symptoms. Gastric emptying was assessed using technetium 99-labeled scrambled eggs.

* Denotes significance from placebo trial ($p < 0.05$) using paired t test and from control group ($p < 0.05$) using nonparametric t test.

TABLE 3. *Effect of Long-term Treatment with Octreotide Acetate on Biochemical Parameters and on Weight Gain*

		After Treatment	
Parameter	Before Treatment	3 months (n = 10)	15 months (n = 8)
Glucose (mg/dL)	95 ± 5	90 ± 6	99 ± 4
Total protein (g/dL)	6.6 ± 0.2	6.6 ± 0.1	7.6 ± 0.2
Albumin (g/dL)	3.9 ± 0.1	3.9 ± 0.1	4.4 ± 0.2
Total bilirubin (mg/dL)	0.3 ± 0.006	0.6 ± 0.4	0.3 ± 0.06
Cholesterol (mg/dL)	179 ± 13	173 ± 9	215 ± 7
LDH (I.U.)	192 ± 17	203 ± 7	187 ± 8
SGOT (I.U.)	29 ± 4	23 ± 3	22 ± 2
Weight gain (% of body weight)	—	7.2 ± 1.2	11 ± 1.3*

* Denotes significance from pretreatment and 3-month periods, each at $p < 0.01$.

The data obtained from the present study and another one from this laboratory[25] emphasized the importance of hormones in mediating the symptomatology of early and late dumping. They also indicate that the systemic symptoms of early dumping are unlikely to be related to changes in either plasma vasoactive intestinal peptide, gastrin, or motilin. None of these hormones were altered in the dumping patients during the placebo trial or in the postgastrectomy nondumping controls. The plasma level of pancreatic polypeptide, neurotensin, and glucagon were markedly elevated during the placebo trial and their levels were suppressed with octreotide pretreatment. It is plausible that these changes implicate a role for these peptides as causative agents in the development of dumping symptoms. However the data obtained in the control group suggest that pancreatic polypeptide does not play a major role in the development of dumping symptoms. The increases in plasma levels of this hormone in response to the breakfast meal in the control group were similar to those seen in the dumping patients while receiving the placebo trial. Furthermore the changes in plasma glucagon also are unlikely to be responsible for the appearance of dumping symptoms in response to the high carbohydrate meal. Glucagon, albeit in pharmacologic doses, is known to decrease gastrointestinal motility and to result in atony.[26] Taken together our data suggest that neurotensin plays a major role in the development of the dumping syndrome. Neurotensin was shown to influence gastrointestinal motility of both the upper and lower intestinal tracts.[27] Infusion of this hormone in humans also was shown to increase the intestinal motility index of the colon and result in diarrhea.[28]

Several other causative agents, not measured in the present study, also were implicated in the development of the syndrome, including kallikrein[29] and serotonin.[7,8] The problem with isolating all of these factors lies in our ability to measure the site at which they exert their biologic activity. In this and other studies, the changes in plasma hormones were measured in the peripheral circulation. This, however, does not preclude the possibility that the symptoms of dumping may be directly related to the actions of gastrointestinal peptides *via* paracrine, autocrine, neural, or luminal routes. More conclusive evidence for implicating any of the above factors will have to await further trials, in which the development of symptoms is monitored during the infusion of such agents, singly or in combination, or when their endogenous secretions are either selectively stimulated or blocked.

The exact mechanism by which octreotide acetate improved the early symptoms of dumping remains unclear. Recent evidence suggests that the peptide-inhibitory effect of octreotide acetate results in a delay in the upper gastrointestinal motility.[30] Octreotide acetate has been shown to decrease the frequency and amplitude (motility index) of contractions in the gastric remnant and in the attached proximal small bowel. In addition it changes the motility of the upper gastrointestinal tract from a fed to a fasted pattern.[25] These changes can thus result in a delay in gastric emptying, which, in turn, is expected to retard the transit of the hyperosmolar meal from the gastric remnant into the small intestine, thus preventing the initiation of dumping. The overall effects lead to decreased incidence of abdominal cramps, borborygmi, intestinal hurry, and diarrhea. The improvement in the two patients with late dumping symptoms can be attributed to the effects of octreotide acetate in preventing the increase in plasma insulin in response to the high carbohydrate meal. This, in turn, prevented the development of late-onset reactive hypoglycemia.

Long-term treatment of patients with severe dumping symptoms, using three to four daily injections of octreotide acetate, was very gratifying. Subjectively all of the patients reported continued diminution of symptoms while using the lowest possible effective dose given 30 minutes before each meal. Seven patients who were crippled by their symptoms before treatment have now returned to full- or part-time employment. The use of this drug has enabled patients to no longer dread travel outside their homes for fear of disabling diarrhea. Weight gain occurred in all patients, which confirms the subjective reports given by these patients. There were no adverse effects noted with long-term treatment with the analog during a 15-month period. Three patients on octreotide acetate treatment complained of diarrhea shortly after awakening in the morning. This was relieved by administering a dose of the analog immediately before bedtime.

A double-blind prospective trial has shown that octreotide acetate is remarkably effective in the acute treatment of early and late symptoms in patients with severe postgastrectomy dumping syndrome. Long-term treatment was successful and, most importantly, had no major side effects. The mechanism of action of this analog appears to be a reduction of the gastrointestinal motility, probably mediated by inhibition of the release of several humoral agents, most notably neurotensin.

Acknowledgments

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Reperfusion Inhibits Elevated Splanchnic Prostanoid Production After Hemorrhagic Shock

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The effect of reperfusion following hemorrhagic shock on splanchnic prostanoid release was studied. Anesthetized male rats were bled to a mean arterial blood pressure of 30 mmHg for 30 minutes and either killed or treated with shed blood for 60 minutes and then killed. The superior mesenteric arterial bed was cannulated and perfused *in vitro* with oxygenated Krebs. Collected venous effluent (up to 180 minutes) was analyzed for 6-keto-$PGF_{1\alpha}$ (PGI_2 metabolite), PGE_2, $PGF_{2\alpha}$, and thromboxane B_2 by radioimmunoassay in shock, shock plus reperfusion, and sham groups. The major prostanoid released was 6-keto-$PGF_{1\alpha}$ and was three times higher in the shock group compared to the sham group ($p < 0.05$). Reperfusion of shed blood abolished the increase in 6-keto-$PGF_{1\alpha}$ found in the shock group ($p < 0.05$). These data show that the attempt of the rat splanchnic bed to compensate for hemorrhagic shock by increasing release of PGI_2 (potent vasodilator) was abolished during reperfusion of blood.

THE GASTROINTESTINAL TRACT has been described as the motor organ in the production of multiple-organ failure. This hypothesis describes alterations in the gastrointestinal mucosal barrier following hemorrhagic shock and resuscitation. Disruption of the mucosal barrier allows bacterial translocation and systemic release of bacterial toxins. These bacterial products contribute to multiple-organ failure and subsequent death.[1–4] The factors that alter splanchnic blood flow during acute hemorrhagic shock and subsequent resuscitation are not known.

Splanchnic vascular prostanoids (PGs) are locally produced paracrine substances that are thought to be one of several factors contributing to regulation of splanchnic vascular flow.[5] These factors include age, sex, dietary lipids, sympathetic tone, ischemia, hormones, and shock.[5–22] These factors can act as stimuli for the release of either vasodilator or vasoconstrictor PGs. The resulting balance of potent vasoactive PGs represents one important factor that contributes to the overall vascular tone of the splanchnic vascular bed.

Recently we compared splanchnic PG release in acute hemorrhagic shock to sham-operated controls *in vitro* in the rat. In this study rats were subjected to hemorrhagic shock without reperfusion of shed blood to determine specifically if the splanchnic bed can compensate for decreased flow secondary to the shock by release of vasodilator prostanoids. Hemorrhagic shock markedly increased the release of PGI_2 (potent vasodilator) but not thromboxane B_2 (TxB_2), PGE_2, or $PGF_{2\alpha}$ when compared to sham-operated controls.[13]

This study examines the hypothesis that the capability of the splanchnic vascular bed to compensate for shock by release of PGI_2 is inhibited by reperfusion of the shed blood. This study will use the technique of *in vitro* perfusion of the rat superior mesenteric artery with its viscera in continuity (splanchnic vessels and small intestine [SV + SI]). This technique allows accurate determination of alterations in endogenous prostanoid release from the superior mesenteric arterial bed without contamination with exogenous sources.

Materials and Methods

Preparation of Shock Rat Model

Male Sprague-Dawley rats weighing approximately 300 g were used for all studies. Regulations of The University of Texas Medical School at Houston for the care and use of animal subjects were followed rigidly. All animals were fasted overnight and anesthetized by methoxyflurane inhalation. The necks and groins were shaved and washed with providine iodine and 70% ethanol. The right com-

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mon carotid artery and the right femoral artery were cannulated with PE-50 and PE-20 polyethylene cannulas, respectively. The carotid artery catheter was attached to a pressure transducer (Deseret Model 8000) and connected to a Keithley 500 system (Keithley AMM1) and interfaced to an IBM PC/XT computer. Arterial pressure and pulse were monitored continuously and stored throughout the study period using this equipment. Animals received 50 units of heparin and hypovolemic shock was induced in all animals by withdrawing a sufficient volume of blood to reduce the mean arterial pressure to 30 mmHg (acute hemorrhagic shock group, SK). This level of shock was maintained for 30 minutes by withdrawing or infusing shed blood as required. The animals of the SK group were killed at this time. The animals in the SK + R group (acute shock plus perfusion) were treated with the shed blood, allowed to recover for 60 minutes, and then killed. Instrumented but nonshocked animals served as controls for both groups (SK + SM, SK + R + SM).

Preparation of Rat Isolated Mesenteric Perfusion

The technique of rat isolated splanchnic perfusion was described previously by our laboratory and is a modification of the technique described by McGregor.[13,23–25] A midline laparotomy was performed after the abdomen was washed with providine iodine. The superior mesenteric artery was isolated, rapidly cannulated with PE-50 tubing, and removed with its terminal splanchnic vessels and end organ (intestine, SV + SI). The ends of the bowel were cannulated and vented outside the warming apparatus to avoid distention. The SV + SI was perfused at 3 mL/minute using a Cole-Parmer peristaltic pump (Cole-Parmer Instrument Co., Chicago, IL) with oxygenated (pO_2 460 ± 10 mmHg) Krebs-Henseleit buffer pH 7.4 at 37 C. The perfusion pressure was monitored constantly *via* a side arm of the arterial cannula using a Statham pressure transducer (Grass Instruments, Quincy, MA). The splanchnic venous effluent was collected after 15, 30, 60, 90, 120, 150, and 180 minutes of perfusion in the SK, SK + SM, SK + R, and SK + R + SM groups. Each sample was collected, placed in siliconized microcentrifuge tubes, and immediately frozen at −40 C until assayed. Radioimmunoassays for 6-keto-$PGF_{1\alpha}$ (stable metabolite of PGI_2), thromboxane B_2 (stable metabolite of thromboxane A_2, TxB_2), $PGF_{2\alpha}$, and PGE_2 were performed within a 2-week period of each experiment.

Cyclooxygenase inhibition by indomethacin was used as a control to confirm the specificity of the radioimmunoassay in the shock group. We have previously shown that indomethacin treatment decreased basal splanchnic prostanoids by approximately 70%.[25] In the current study indomethacin (20 μg/mL) was added to the perfusate in the shock group by a separate infusion line and samples were collected as described above.

Radioimmunoassay

Radioimmunoassays were performed as previously described.[13,25] 6-keto-$PGF_{1\alpha}$, thromboxane B_2 (TxB_2), $PGF_{2\alpha}$, and PGE_2 were measured from the unextracted effluent perfusate by radioimmunoassay. The assay reaction occurred in a volume of 300 μL consisting of 100 μL each of sample (or standard), radiolabeled tracer ligand, and specific antisera, all incubated at 27 C for 2 hours. Bound and free fractions of ligand were separated by adding 500 μL dextran-coated charcoal (DCC, see below) followed by centrifugation at 1000*g* (2400 rpm) for 20 minutes. The supernatant containing the antibody-bound component then was decanted. Five milliliters of Aquasol (NEN Research Products, Boston, MA) was added and beta emissions were counted on an LKB Rack Beta 1217 scintillation counter (LKB Instruments, Inc., Gaithersburg, MD). All samples and standards were assayed in duplicate.

The assay buffer, used to dilute the antisera, radiolabeled ligands, and in preparing DCC consisted of 50 mmol/L (millimolar) TRIS pH 7.5 (Trizma base and HCl, Sigma Chemical Co., St. Louis, MO) with 0.1% biologic grade gelatin (porcine, bloom number = 300; Aldrich, Milwaukee, WI) and 0.01% sodium azide (Sigma). Dextran-coated charcoal was 7 mg Norite-A activated carbon (Aldrich) and 0.360 mg Dextran (T-70, Aldrich) per milliliter of assay buffer.

Unlabeled PGE_2, 6-keto-$PGF_{1\alpha}$, $PGF_{2\alpha}$, and TxB_2 (Sigma) were kept refrigerated at 100 ng/mL in assay buffer (TRIS). For each assay serial dilutions in Krebs buffer were made for seven standards ranging from 2.7 to 2000 pg/100 μL. Tritiated standards (Amersham Co., Arlington Heights, IL) of 0.1 mCi/mL had specific activities of 157 Ci/mmole 6-keto $PGF_{1\alpha}$, 178 Ci/mole TxB_2, 179 Ci/mole $PGF_{2\alpha}$, and 184 Ci/mmole PGE_2.

Antisera was obtained in lyophilized form from Dr. Lawrence Levine, Department of Biochemistry, Brandeis University (TxB_2 and 6-keto $PGF_{1\alpha}$) and Advanced Magnetics (Cambridge, MA) (PGE_2, $PGF_{2\alpha}$). Dilutions in assay buffer of 1:12,000, 1:18,000, 1:5,000, 1:6000 for 6-keto-$PGF_{1\alpha}$, TxB_2, PGE_2, and $PGF_{2\alpha}$, respectively, were used to obtain 40% to 60% binding of a zero standard ‘blank.’ Cross-reactivity of antisera from Dr. Levine has been published: for 6-keto $PGF_{1\alpha}$, less than 1% to $PGF_{2\alpha}$, PGD_2, TxB_2, and 13,14-H_2-PGE_2;. for TxB_2 antisera, less than 1% $PGF_{2\alpha}$, PGD_2, 6-keto $PGF_{2\alpha}$, 13,14-H_2-PGE_2, and 6-keto $PGF_{1\alpha}$[26]; cross-reactivity of PGE_2 and $PGF_{2\alpha}$ antisera given by Advanced Magnetic for PGE_2 was 50% to PGE_1, 6% to PGA_2, 3% to PGA_1, 1.3% to $PGF_{2\alpha}$, less than 1% to TxB_2 and 6-keto $PGF_{1\alpha}$; for $PGF_{2\alpha}$, 100% to $PGF_{1\alpha}$, 1.1% to PGE_1, 1.1% to 6-keto-$PGF_{1\alpha}$, 0.5% to TxB_2, 0.3% to PGE_2, less than 0.1% to PGD_2, less than 0.1% to PGA_2, less than 0.1% to PGA_1, less than 0.1% to PGB_1, less than

0.1% to PGB_2, less than 0.1% to 13,14-Dihydro-15-keto-$PGF_{2\alpha}$, and less than 0.1% to 6-keto-PGE_1.

All samples and standards were measured in duplicate. The standard curve was constructed using the smooth-spline function (RIA computer package SecuRIA, Packard, Downers Grove, IL). Unbound, unabsorbed tracer (referred to as 'nonspecific binding') was quantified in tubes containing only labeled ligand and DCC. Interassay and intra-assay variation was 7% to 9% for 6-keto-$PGF_{1\alpha}$, $PGF_{2\alpha}$, and TxB_2, while variation was 14% to 15% for PGE_2. Sensitivity, the amount of unlabeled standard causing 10% reduction from maximal binding of the blank, was approximately 8 pg. (This was equivalent to 240 pg/minute at the flow rate of 3 mL/minute used in these experiments.

Statistical Analysis

Data is reported as mean ± SEM (ng/min) for all groups. One-way analysis of variance and analysis by Duncan's *post hoc* test were used for all groups, except where indicated in Table 1. Differences in mean values were considered significant at a p value for type I error of less than 0.05.

Results

As previously reported the perfused SV + SI from the SK + SM group released 6-keto-$PGF_{1\alpha}$, PGE_2, $PGF_{2\alpha}$, and TxB_2 at all time periods measured. Prostanoid release was maximal at 15 and 30 minutes of perfusion and decreased to a stable baseline at 60 minutes of perfusion until the 180-minute time of perfusion when prostanoid release again increased (Figs. 1 to 4, Table 1). 6-keto-$PGF_{1\alpha}$ was the major prostanoid released in the SK + SM group and was 3.5 to 6 times higher than the other PGs at 15 and 30 minutes of perfusion (Fig. 1, Table 1).

Prostanoid release was increased two or more times in the SK group compared to the SK + SM group at all time periods studied (Figs. 1 to 4, Table 1), as previously described.[13] 6-keto-$PGF_{1\alpha}$ release was increased significantly in the SK group at 15 and 30 minutes of perfusion (Fig. 1, Table 1). Cyclooxygenase inhibition by indomethacin (20 μg/mL; Sigma) decreased SK released of 6-keto-$PGF_{1\alpha}$, TxB_2, and $PGF_{2\alpha}$ by 60% to 70% at 15 and 30 minutes of perfusion, whereas PGE_2 release was decreased by only 15% to 33% (Table 1). The indomethacin data suggests that acute shock increased release of 6-keto-$PGF_{1\alpha}$ and to a lesser extent TxB_2 and $PGF_{2\alpha}$ release and not PGE_2.

The SK + R + SM group released prostanoids at all time periods and was similar to the SK + SM group (Figs. 1 to 4). 6-keto-$PGF_{1\alpha}$ was the major PG released and was two or more times higher than the other PGs (Figs. 1 to 4). Treatment of the SK animals with shed blood followed by recovery for 60 minutes completely abolished the general increase in prostanoid release described in the SK group. In fact 6-keto-$PGF_{1\alpha}$ release was decreased four times in the SK + R group when compared to the SK group (Fig. 1, Table 1).

Perfusion pressure was not altered in the SK or SK + R groups when compared to the sham groups.

Conclusions

The gastrointestinal tract has been hypothesized to play a major role in the evolution of the clinical syndrome of multiple-organ failure. This hypothesis encompasses the notion that clinical hemorrhagic shock and resuscitation

TABLE 1. *The Effect of Acute Hemorrhagic Shock (SK) and Acute Shock + Perfusion (SK + R) on Rat Splanchnic Prostanoid Release*

Group/Time	*N*	6-keto*	TxB_2†	PGE_2	$PGF_{2\alpha}$
15 Minutes					
SK + SM	8	7.6 ± 1.6	1.2 ± 0.2‖	2.1 ± 0.2‖	2.1 ± 0.4‖
SK	10	19.0 ± 4.0§	3.5 ± 1.6**	4.5 ± 1.2**	5.3 ± 2.2**
SK + SM + R	8	6.6 ± 1.1	1.7 ± 0.2‖	3.8 ± 0.3	2.3 ± 0.3‖
SK + R	6	4.5 ± 0.5§	1.8 ± 0.2	3.4 ± 0.4	1.9 ± 0.1
SK + Indo	4	8.4 ± 2.4¶	1.0 ± 0.3	3.0 ± 0.6	1.6 ± 0.4
30 Minutes					
SK + SM	8	4.0 ± 1.0	0.7 ± 0.1	1.1 ± 0.2	1.4 ± 0.3
SK	10	11.0 ± 2.8	1.1 ± 0.4**	2.1 ± 0.5**	2.7 ± 0.7**
SK + SM + R	8	3.5 ± 0.6	1.0 ± 0.1	2.6 ± 0.4	1.7 ± 0.1
SK + R	6	2.0 ± 0.2§	0.9 ± 0.1	1.8 ± 0.3	1.3 ± 0.1
SK + Indo	4	3.2 ± 0.7¶	0.4 ± 0.1	0.8 ± 0.5	0.7 ± 0.2#

* 6-keto, 6-keto-$PGF_{1\alpha}$.

† TxB_2, thromboxane B_2.

‡ Significant at $p < 0.05$ compared to SK + SM in same group and time.

§ Significant at $p < 0.05$ compared to SK in same group and time.

‖ Significant at $p < 0.05$ compared to SK + SM or SK + SM + R 6-keto.

¶ Significant at $p < 0.05$ compared to SK 6-keto (Student's unpaired t test).

# Significant at $p < 0.05$ compared to SK $PGF_{2\alpha}$ (Student's unpaired t test).

** Significant at $p < 0.05$ compared to SK 6-keto.

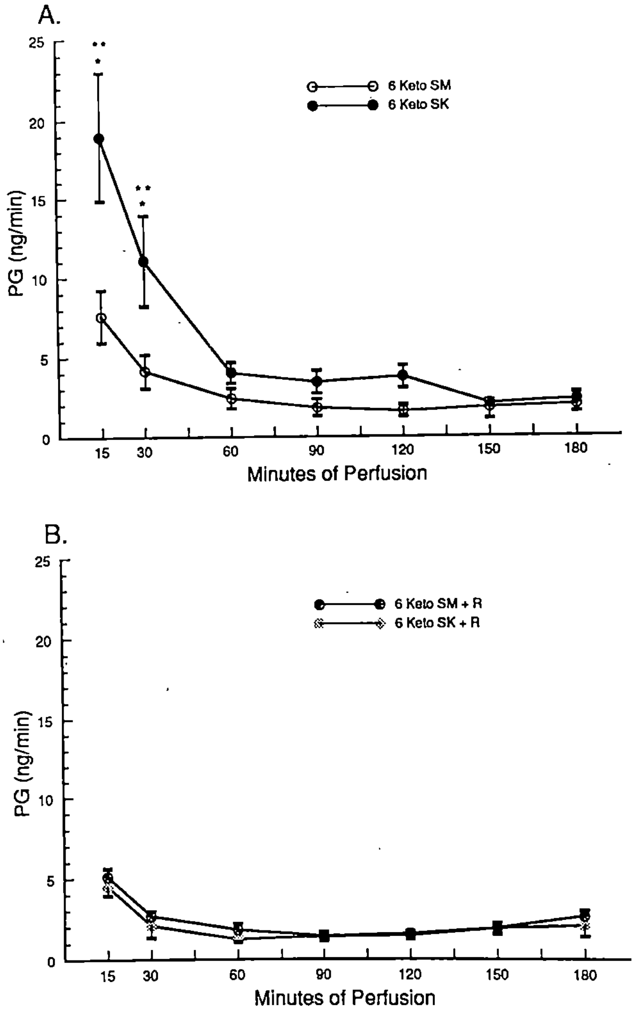

FIG. 1. Comparison of 6-keto-$PGF_{1\alpha}$ output from the perfused male rat splanchnic vessels and small intestine (SV + SI) in (A) acute hemorrhagic shock (SK) and sham groups (SK + SM) and (B) SK plus reperfusion (SK + R) and sham groups (SK + R + SM). All animals were perfused for 180 minutes. Values are given as mean ± SEM. (A) n = 10 SK, n = 8 SK + SM; * indicates $p < 0.05$ compared to SK + SM. (B) n = 6 SK + R, n = 8 SK + R + SM; ** indicates $p < 0.05$ compared to SK + R + SM.

lead to a decrease in splanchnic blood flow. Decreased splanchnic flow affects the metabolically more active intestinal mucosa than the muscularis. Mucosal injury leads to a breakdown of the mucosal barrier to enteric bacteria, which then 'translocate' to the liver, regional lymph nodes, and so on. Release of toxic bacterial products affects normal physiologic function of the liver, lungs, kidneys, and heart and leads to progressive multiple-organ failure and subsequent death of the patient.[1-4] The factors that regulate alterations in splanchnic flow in this scenario are not known.

Elevations in serum levels of all prostanoids have been described following several types of experimental shock.[13-22] Most of these studies have used endotoxin shock, sepsis and cecal ligation, and puncture as models of shock. Hemorrhage, splanchnic artery occlusion, and cardiac tamponade are other etiologies of shock developed to delineate this question. The studies performed since the discovery of PGI_2, a potent vasodilator, and thromboxane A_2, a potent vasoconstrictor, have implicated an increased release of TxB_2 with mortality rates after experimental shock in animals.[14-15] Inhibition of increased serum TxB_2 levels with thromboxane synthetase inhibitors, cyclooxygenase inhibitors, and alterations in essential fatty acids decreased the number of shock-induced deaths. These studies have left several important questions unanswered. What is the source of enhanced prostanoid synthesis and

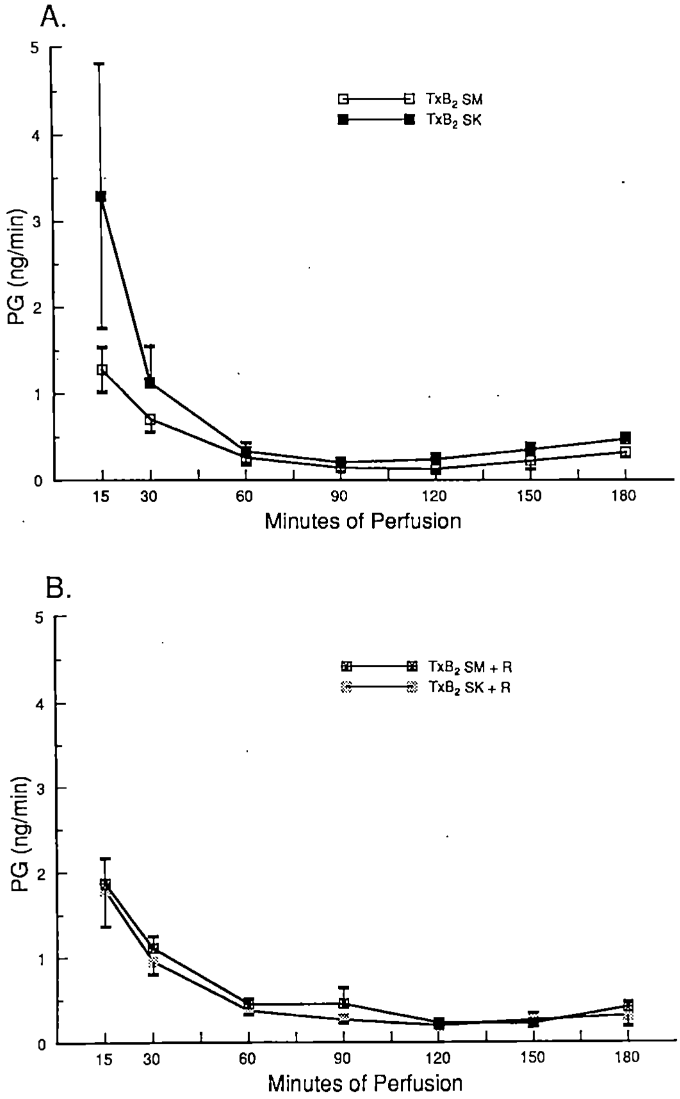

FIG. 2. Comparison of thromboxane B_2 output from the perfused male rat splanchnic vessels and small intestine (SV + SI) in (A) acute hemorrhagic shock (SK) and sham groups (SK + SM) and (B) SK plus reperfusion (SK + R) and sham groups (SK + R + SM). All animals were perfused for 180 minutes. Values are given as mean ± SEM. (A) n = 10 SK, n = 8 SK + SM. (B) n = 6 SK + R, n = 8 SK + R + SM.

release following shock? Does PGI_2 play a role in alterations in vascular flow during shock?

The data from this study supports our previous work that examined alterations in splanchnic prostanoid release after acute hemorrhagic shock. This preliminary study showed that treatment of the rats with acute hemorrhagic shock increased prostanoid release with the most substantial increase in 6-keto-$PGF_{1\alpha}$ (PGI_2) when compared to sham-operated controls.[13] We attributed the marked increase in SK 6-keto-$PGF_{1\alpha}$ (PGI_2, a potent vasodilator) release as a compensatory mechanism of the rat splanchnic vascular bed to early acute shock and hypovolemia to maintain splanchnic flow. Previous data from our laboratory also demonstrated the splanchnic visceral bed (intestine) and not the splanchnic vessels as the site of synthesis of 90% of TxB_2 and PGE_2 released and 60% to 80% of the 6-keto-$PGF_{1\alpha}$ released in our model.[25] In the context of these data, we suggest that the attempt at compensation for decreased splanchnic visceral blood flow by increasing PGI_2 release is located within the intestine itself. In the present study, reperfusion of the shed blood after acute hemorrhage totally abolished the rise in prostanoid levels described in the SK group. These data suggest that reperfusion inhibits the attempt by the splanchnic visceral bed to compensate for acute hemorrhage by increasing synthesis and release of PGI_2.

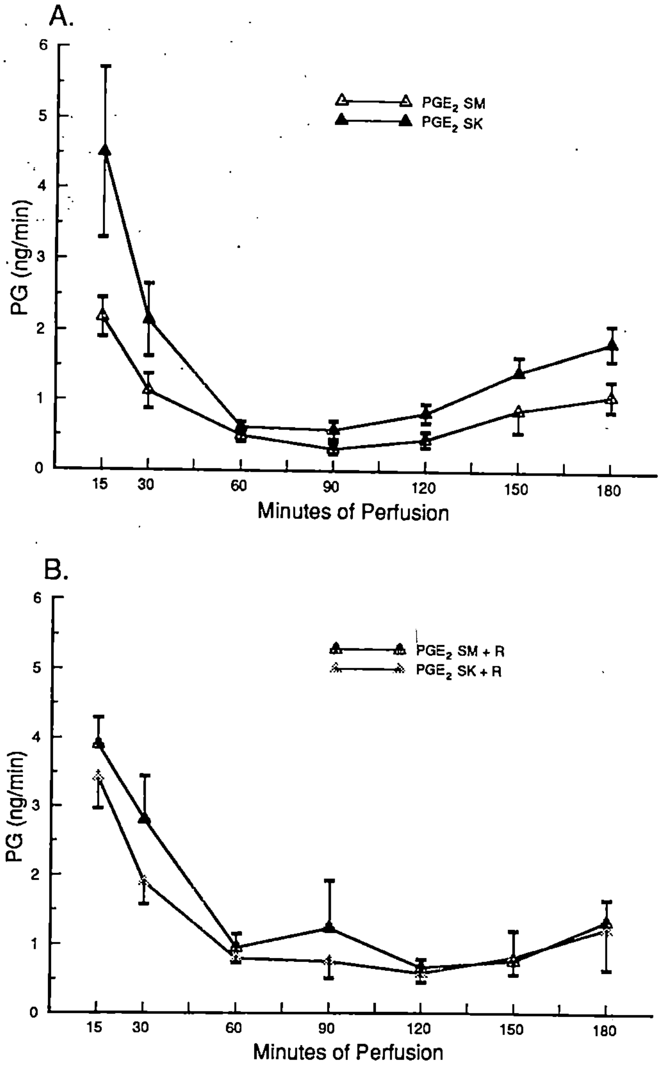

FIG. 3. Comparison of PGE_2 output from the perfused male rat splanchnic vessels and small intestine (SV + SI) in (A) acute hemorrhagic shock (SK) and sham groups (SK + SM) and (B) SK plus reperfusion (SK + R) and sham groups (SK + R + SM). All animals were perfused for 180 minutes. Values are given as mean ± SEM. (A) n = 10 SK, n = 8 SK + SM; (B) n = 6 SK + R, n = 8 SK + R + SM.

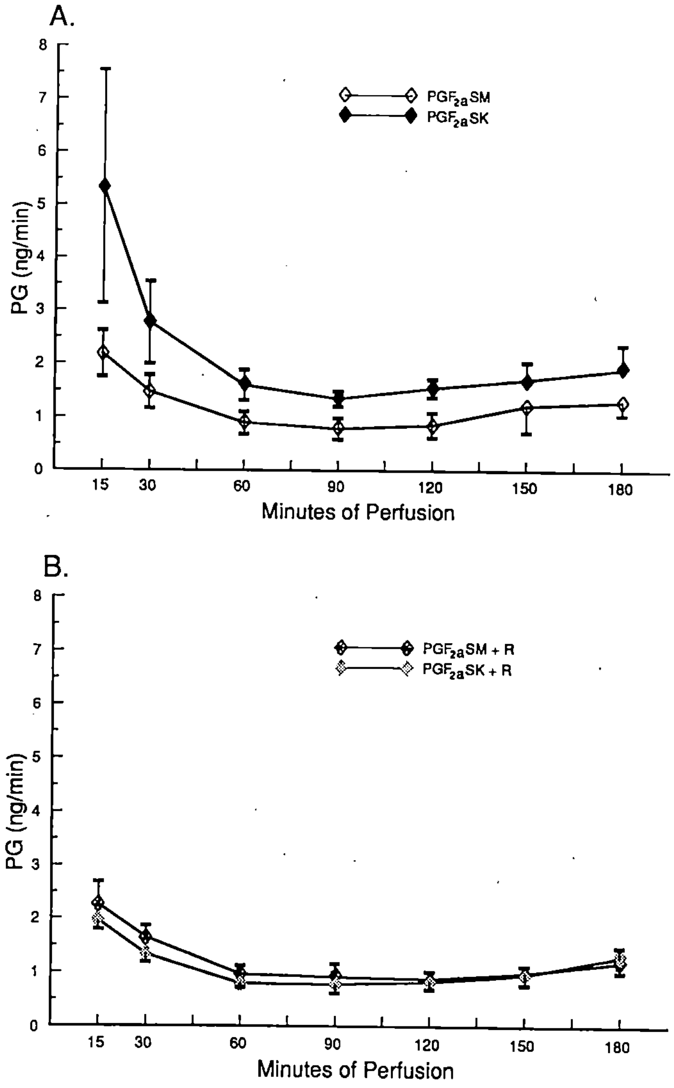

FIG. 4. Comparison of $PGF_{2\alpha}$ output from the perfused male rat splanchnic vessels and small intestine (SV + SI) in (A) acute hemorrhagic shock (SK) and sham groups (SK + SM) and (B) SK plus reperfusion (SK + R) and sham groups (SK + R + SM). All animals were perfused for 180 minutes. Values are given as mean ± SEM. (A) n = 10 SK, n = 8 SK + SM; (B) n = 6 SK + R, n = 8 SK + R + SM..

We believe that one of the factors responsible for reperfusion inhibition of increased prostanoid release following acute hemorrhage may be related to the production of lipid peroxides or oxygen-derived free radicals. Oxygen-derived free radicals and lipid peroxides have been described as one type of mediator of tissue injury following ischemia. The hypothesis implicating oxygen-derived free radicals in tissue injury describes conversion of xanthine dehydrogenase to the superoxide-producing oxidase. Xanthine oxidase catalyses production of accumulated hypoxanthine (ATP metabolite) and oxygen to xanthine and superoxide radicals.[27–30] The superoxide radicals are believed to alter cell viability by peroxidation of lipid components. Lipid peroxides have been shown to inhibit cyclooxygenase and more specifically prostacyclin synthetase.[31] We hypothesize that oxygen free radicals or other lipid peroxides formed during ischemia are introduced into the splanchnic visceral bed during reperfusion. These toxic metabolites alter splanchnic PGI$_2$ biosynthesis and release, abolishing the attempt of the splanchnic visceral bed to maintain blood flow following acute hemorrhagic shock.

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Evidence for Tumor Necrosis Factor-induced Pulmonary Microvascular Injury After Intestinal Ischemia–Reperfusion Injury

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Acute lung injury characterized by increased microvascular permeability is one feature of multiple-organ system failure and the adult respiratory distress syndrome. Intestinal ischemia–reperfusion injury has been linked to this type of acute lung injury. The purpose of these experiments was to examine the pathogenic mediators that link the two processes, with particular emphasis on the roles of endotoxin and tumor necrosis factor α (TNFα). Previously described characteristics of the acute lung injury in this rat model of intestinal ischemia–reperfusion include pulmonary neutrophil sequestration, depletion of lung tissue ATP, alveolar endothelial cell disruption, and increased microvascular permeability. Plasma levels of TNF in the systemic circulation of sham-operated animals and those with intestinal ischemic injury less than 60 minutes in duration were very low or undetectable. Intestinal ischemia for 120 minutes was associated with TNF elevation to 1.19 ± 0.50 U/mL. Reperfusion for periods of 15 and 30 minutes generated 5- to 10-fold increases in circulating TNF levels (6.61 ± 3.11 U/mL, $p > 0.05$ and 10.41 ± 5.41 U/mL, $p = 0.004$ compared to sham); however this increase in circulating TNF was transient and largely cleared within 60 minutes after initiating reperfusion. Portal vein endotoxin levels were found to increase significantly before the appearance of TNF in systemic plasma, suggesting that gut-derived endotoxin may induce TNF release from hepatic macrophages into the systemic circulation. Anti-TNF antibody attenuated the increase in pulmonary microvascular permeability in this preparation but did not prevent pulmonary neutrophil sequestration. These observations suggest that endotoxin and TNF have pathogenic roles in this acute lung injury, but that mechanisms of adherence of neutrophils to endothelial cells independent of TNF may be involved. The accumulation of neutrophils in the lung but the prevention of a vascular permeability increase in the presence of antibody to TNF may imply an *in vivo* role for TNF in the process of neutrophil activation. These studies provide additional evidence of the importance of the endogenous inflammatory mediators in the development of systemic injury in response to local tissue injury.

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ACUTE LUNG INJURY associated with activation of an endogenous inflammatory response is characteristic of the adult respiratory distress syndrome (ARDS) and other causes of acute respiratory failure. A variety of diverse injuries remote from the pulmonary capillary endothelial bed may initiate this process. These include cutaneous thermal injury,[1,2] acute pancreatitis,[3,4] sepsis,[5] and intestinal ischemia–reperfusion injury.[6] Evidence that the neutrophil and other phagocytic cells participate in this systemic process is derived from many sources.[7,8] It appears that a variety of plasma factors (*e.g.*, complement products, cytokines, platelet-activating factor) are generated locally at a site of tissue injury and subsequently distributed systemically. These factors are associated with activation, sequestration, and adherence of phagocytic cells at particular target sites such as the alveolar capillary bed. In addition alveolar endothelial cells are no longer thought to be simply passive targets. Endothelial cell adhesive molecules for leukocytes are known to be induced by endotoxin as well as by cytokines such as tumor necrosis factor α (TNFα) and interleukin 1 (IL-1).[9]

Tumor necrosis factor in particular is implicated as a proximal mediator in the pathogenesis of multiple-organ system tissue injury associated with septic shock. Tracey et al.[10] first reported multiple-organ injury in rats after the intravenous administration of recombinant TNF. The features of the pulmonary injury in these original experiments included marked neutrophil margination, pneumonitis, and arterial thrombosis with aggregations of neutrophils. Others subsequently confirmed a pathogenic role for both TNF and neutrophils in this type of inflam-

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matory lung injury. Stephens et al.[11] recently provided evidence that neutrophil depletion is protective against TNF-mediated acute lung injury in guinea pigs.

We have described an acute lung injury in rats following intestinal ischemia–reperfusion that shares some characteristics of TNF- and neutrophil-induced lung injury. Features include alveolar capillary endothelial cell injury with increased microvascular permeability, depletion of tissue adenosine triphosphate (ATP), and neutrophil sequestration.[6] Although it is appealing to speculate that this injury is mediated through the process of neutrophil activation and adherence to endothelial cells in alveolar capillaries, neutrophil depletion studies have not been helpful because the initiating event (intestinal ischemia–reperfusion injury) depends on the participation of neutrophils. The purpose of these studies was to evaluate the relationship of gut-derived endotoxin, TNF, and the neutrophil in the pathogenesis of this lung injury associated with intestinal ischemia–reperfusion injury. The data provide support for the hypothesis that ischemia–reperfusion injury generates release of endotoxin from the gut into portal venous plasma, thereby stimulating TNF production by hepatic macrophages. Tumor necrosis factor elevation in the systemic circulation may, in turn, initiate pulmonary neutrophil sequestration and acute lung injury. An anti-TNF antibody was found not to prevent pulmonary neutrophil sequestration but did attenuate the endothelial cell injury, suggesting that the injury requires TNF for full expression but that mechanisms of adherence of neutrophils to endothelial cells independent of TNF may be involved.

Methods

Animal Model

Pathogen-free male Sprague Dawley rats weighing 100 to 150 g (Charles River, Portage, MI) were used for all experiments. Experimental protocols were approved by the University of Michigan Committee on Use and Care of Animals. A detailed description of the model has been reported.[6] Briefly, experimental animals were allowed water only for 24 hours before use; anesthesia was provided with intramuscular (IM) ketamine hydrochloride (100 mg/kg). Following midline laparotomy, intestinal ischemia was achieved by application of a noncrushing microvascular clip to the superior mesenteric artery (SMA). Reperfusion was allowed by clip removal at a second laparotomy after a second anesthetic (ketamine hydrochloride, 50 mg/kg, IM) and confirmed by laser Doppler determination of mucosal blood flow. Periods of intestinal ischemia ranged from 15 to 120 minutes; similarly periods of reperfusion ranged from 15 to 120 minutes. The animals were killed by exsanguination and both lung tissue and blood samples were obtained for analysis. Sham-operated control animals underwent identical preparation but did not have placement of a microvascular clip on the superior mesenteric artery.

Endotoxin Measurement

After the designated periods of intestinal ischemia and reperfusion, portal venous plasma samples were obtained for analysis of endotoxin content. Analysis was performed using a quantitative chromogenic limulus amoebocyte lysate assay (Q.C.L. 1000, Quantitative Chromogenic LAL, Whitaker Bioproducts, Walkersville, MD). The assay depends on bacterial endotoxin to activate a proenzyme in the limulus amoebocyte lysate that catalyzes the cleavage of p-nitroanaline (pNA) from the colorless substrate. The pNA is assayed spectrophotometrically at 405 nm and provides a quantitative analysis of endotoxin content. Samples were compared to the absorption of serially diluted reference endotoxin standards (*Escherichia coli* endotoxin 0111; B4). Data are expressed as endotoxin units per milliliter ([EU]/mL). (Because the observed fluctuations in endotoxin levels were statistically different on initial evaluation, perchloric acid treatment of plasma was omitted.)

Measurement of Tumor Necrosis Factor α Activity

After the experimental intestinal ischemia and reperfusion injury, inferior vena cava (IVC) plasma samples were obtained for TNF levels. Tumor necrosis factor activity was determined using the WEHI 164, subclone 13-cell line. This bioassay, which depends on the lytic effect of TNF on this mouse fibrosarcoma line, is the most sensitive available assay (capable of detecting approximately 1 pg/mL of TNF).[12,13] Briefly, plasma samples were serially diluted and placed in 96-well microtiter plates (Costar, Cambridge, MA). The WEHI cells were resuspended at 5×10^5 cells/mL in RPMI 1640, 10% fetal calf serum, 1 mmol/L (millimolar) L-glutamine, 0.5 μg/mL actinomycin D (Calbiochem, La Jolla, CA) and added to the diluted test samples (100 μL/well). The plates were incubated at 37 C and 5% CO_2 for 20 hours. Following incubation 20 mL of 3-(4,5-di-methylhiazol-2-yL)-2,5-diphenyltetrazolium bromide (MTT) (5 mg/mL, Sigma, St. Louis, MO) in phosphate-buffered saline was added to each well and the plates were reincubated for 4 more hours. After the second incubation, 100 mL of 0.04 N HCl/isopropanol was added to each well to dissolve the purple formazine crystals. Plates were stored overnight in the dark and then read at 550 nm on a Bio-Kinetics Reader (Bio-Tek Instruments, Inc., Winoski, VT). Readings were compared to a standard curve generated using human recombinant TNF (Cetus Corporation, Emeryville, CA) and data are expressed as units/milliliter. Confirmation of the cytotoxicity of plasma TNF in the positive samples was achieved by neutralization with a polyclonal rabbit antimurine TNF antiserum (anti-TNF antibody) that cross reacts with rat TNF.

Assessment of Pulmonary Microvascular Injury

At the time of initial laparotomy, immediately before SMA occlusion, 1 mL of ^{125}I bovine serum albumin (BSA) (800,000 to 1,000,000 cpm) was injected into the IVC. When the animals were killed, 1 mL of blood was aspirated from the IVC. The heart and lungs were removed *en bloc* and 20 mL of sterile saline was infused into the right ventricle to wash residual blood and ^{125}I BSA from the pulmonary vascular bed. Done quickly, a spontaneous heart beat persisted, the pulmonary parenchyma blanched and the effluent became asanguinous. Both lungs and the 1-mL whole blood sample were weighed and placed in a gamma scintillation counter. The ratio of lung to blood counts per minute was calculated and normalized by the respective weights. The resulting permeability indices are a reliable, quantifiable method for assessing lung microvascular permeability and reflect alveolar endothelial cell injury.[3,4] The ratio is intuitively interpretable. For example a ratio of 0.20 indicates that 20% of the intravascular ^{125}I BSA label has been sequestered in the extravascular compartment during the experimental period. This permeability evaluation has been previously described in detail.[14]

Myeloperoxidase (MPO) Assay

Lung content of myeloperoxidase was measured to quantitate the degree of pulmonary neutrophil sequestration with and without anti-TNF antibody. The method is a modification of the assay described by Goldblum.[15] Using additional animals, the hearts and lungs were removed *en bloc* when the animals were killed and 20 mL of sterile saline were infused into the right ventricle to remove residual blood, as described above. Both lungs were removed from the heart and hilar structures. The lung specimens then were weighed and placed in potassium phosphate buffer with 0.5% hexadecyltrimethyl ammonium bromide and homogenized for 40 seconds (4 × 10 seconds, Brinkmann Tissue Homogenizer, Des Plains, IL). The iced homogenate was then sonicated for 30 seconds (3 × 10 seconds, Sonicater® Heat Systems-Ultrasonics, Inc., Farmingdale, NY) and centrifuged at 12,000*g* for 15 minutes at 4 C. The supernatant was mixed 1:30 (supernatant: assay buffer) and read at 460 nm. The assay buffer consisted of 100 mmol/L potassium phosphate pH 6.0, 0.083 mL H_2O_2 (Sigma; 30% stock diluted 1:100), and 0.834 mL o-dianisidine hydrochloride (Sigma; 10 mg/mL). Myeloperoxidase units were calculated as the change in absorbance over time.

Anti-TNF Antibody

A polyclonal rabbit antimurine-TNF antiserum (anti-TNF antibody) was used to assess the effects of TNF blockade on microvascular lung injury and pulmonary neutrophil sequestration after intestinal ischemia and reperfusion. The antibody neutralizes both recombinant and natural TNF and cross reacts with rat TNF.[16] Experimental animals had 3.5 mg of antibody diluted 1:1 with 1 mL RPMI 1640 and administered intravenously immediately before occluding the superior mesenteric artery. Control animals also were given 1 mL of either normal rat or rabbit serum diluted 1:1 with RPMI 1640.

Statistical Analysis

Data is expressed as mean ± standard error of the mean throughout. A one-way analysis of variance with Tukey's standardized range test was used to analyze the data ($p < 0.05$ was considered significant).

Results

Animal Model

This model of intestinal ischemia and reperfusion produced a time-dependent, progressive intestinal injury that was reversible until the intestinal ischemic period exceeded 60 minutes. The histologic features of this type of intestinal injury have been described by researchers in this and other laboratories.[17,18] An important feature of this model included systemic hemodynamic stability.[6] In addition this ischemia–reperfusion injury to the intestine resulted in acute microvascular injury to the pulmonary vascular bed. Characteristics of this lung injury include an increase in microvascular permeability; a rapid, reversible loss in lung tissue ATP; pulmonary neutrophil sequestration; and histologic evidence of endothelial cell injury.[6] Times of ischemia and reperfusion are designated throughout this report as time of ischemia/time of reperfusion, (*e.g.*, 120/15 represents 120 minutes of ischemia followed by 15 minutes of reperfusion).

Plasma TNF Levels Following Intestinal Ischemia–Reperfusion Injury (Fig. 1)

Plasma TNF levels were measured in systemic blood (IVC) to assess changes after intestinal ischemia–reperfusion injury. The data in Figure 1 illustrate the increases in systemic plasma TNF levels. Tumor necrosis factor levels are at the threshold of detectability in sham-operated animals (0.13 ± 0.09 U/mL). Following 120 minutes of intestinal ischemia without reperfusion, TNF levels remain relatively low (1.19 ± 0.50 U/mL). Reperfusion of the ischemic intestine for 15 minutes results in a fivefold

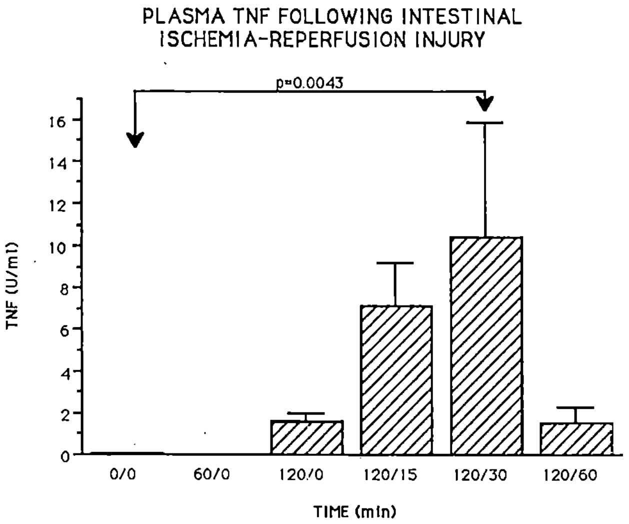

FIG. 1. Plasma TNF levels following intestinal ischemia–reperfusion injury. Ischemia alone produces little increase in plasma TNF levels. Reperfusion for 15 minutes is associated with a fivefold increase and reperfusion for 30 minutes is associated with a maximal (roughly 10-fold) increase in TNF levels. Times on the horizontal axis represent minutes of intestinal ischemia/minutes of intestinal reperfusion, (*e.g.*, 120/15 represents 120 minutes of ischemia and 15 minutes of reperfusion).

increase in TNF levels (to 6.61 ± 3.11 U/mL, $p > 0.05$ compared to sham). Reperfusion for 30 minutes results in a maximal elevation of plasma TNF (10.41 ± 5.41 U/mL, $p = 0.0043$ compared to sham). Rapid clearance of TNF was observed; following 60 minutes of reperfusion, plasma TNF levels diminished to 1.92 ± 1.58 U/mL.

Portal Vein Endotoxin Levels (Fig. 2)

Macrophages challenged with endotoxin elaborate TNF.[19] Intestinal injury induced by ischemia results in the disruption of gut mucosa barrier function and systemic endotoxin release.[20] Because the liver has an abundant population of macrophages, the hypothesis was developed that endotoxin challenge to the liver resulting from intestinal ischemia might elicit significant TNF release from hepatic macrophages. The time course of endotoxin appearance in portal vein plasma in this model therefore was determined. Figure 2 illustrates the findings. Bacteremia did not occur (unpublished data).

No endotoxin was detectable in portal venous blood in sham-operated animals. The initial appearance of endotoxin occurred after 30 minutes of intestinal ischemia (0.075 ± 0.01 EU/mL). Longer periods of ischemia and reperfusion resulted in a progressive increase in portal vein endotoxin content until the maximal elevation was reached after 120 minutes of ischemia and 60 minutes of reperfusion. Plasma samples obtained simultaneously from the inferior vena cava demonstrate the initial increase in endotoxin at 60 minutes of intestinal ischemia (data not shown), after the appearance of endotoxin in portal vein plasma at 30 minutes. It is noteworthy that peak TNF levels occur 90 to 120 minutes after the initial appearance of endotoxin in portal venous plasma. This time frame is consistent with published data regarding the interval required for TNF mRNA to appear after endotoxin challenge.[21]

Lung Microvascular Permeability Changes Associated with Intestinal Ischemia–Reperfusion Injury Following Treatment with Anti-TNF Antibody (Fig. 3)

Tumor necrosis factor is implicated as a mediator of experimental acute lung injury.[10,22] Stephens et al.[11] demonstrated that TNF-mediated acute lung injury in guinea pigs is neutrophil dependent. Lung microvascular permeability was assessed in this intestinal ischemia–reperfusion model following the administration of anti-TNF antibody.

Sham animals (0/0) and experimental animals (120/60 and 120/120) were given either anti-TNF antibody or normal rat or rabbit serum intravenously, and lung microvascular permeability was assessed as above. Figure 3 illustrates the comparisons between groups. Sham-operated animals given anti-TNF antibody or normal serum had no change in permeability. Animals subjected to 120 minutes of intestinal ischemia and 120 minutes of reperfusion and given normal serum had a permeability index of 0.72 ± 0.02 consistent with a severe pulmonary mi-

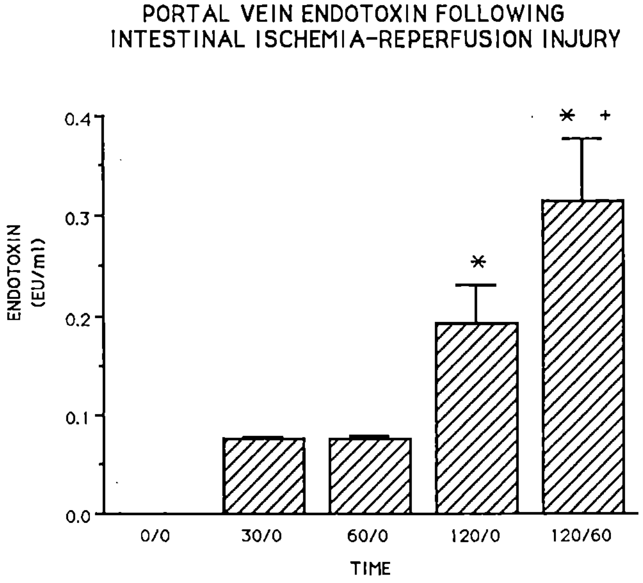

FIG. 2. Endotoxin levels in portal vein plasma following intestinal ischemia–reperfusion injury are shown. Endotoxin appears in portal vein plasma after 30 minutes of ischemia and peaks at 60 minutes after reperfusion). (*$p < 0.05$ compared to sham [0/0], + $p < 0.05$ compared to 30/0 and 60/0).

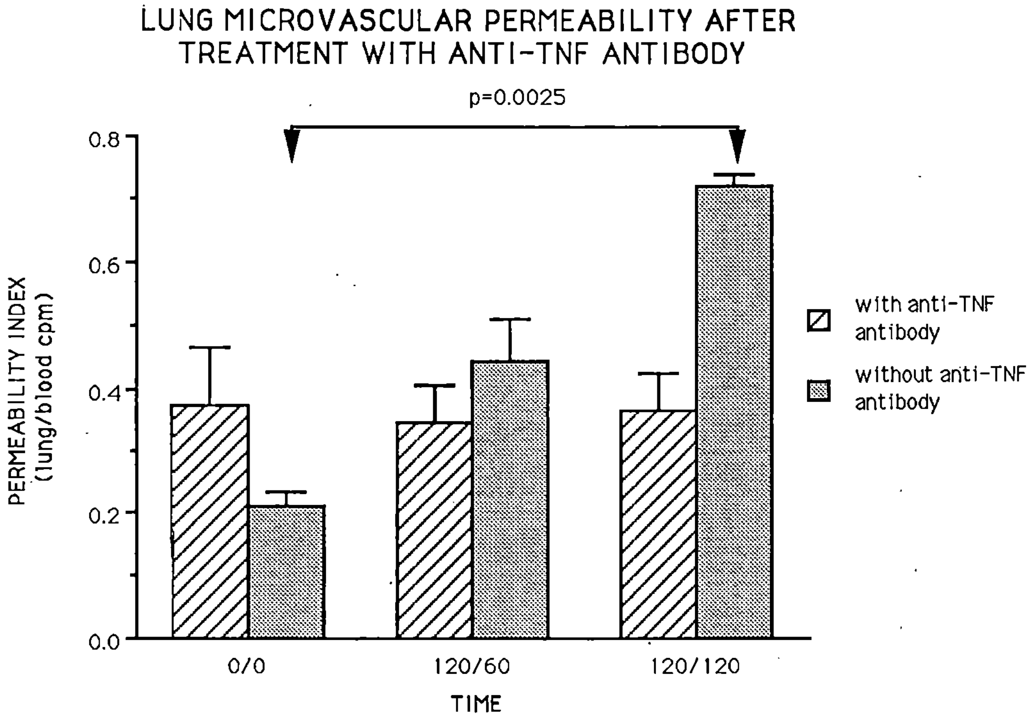

FIG. 3. Lung microvascular permeability increases associated with intestinal ischemia–reperfusion injury are attenuated by pretreatment with anti-TNF antibody. Control (without anti-TNF antibody) and experimental (with anti-TNF antibody) groups for each time point are shown. Times on the horizontal axis represent minutes of intestinal ischemia/minutes of intestinal reperfusion, (*e.g.*, 120/60 represents 120 minutes of ischemia and 60 minutes of reperfusion).

crovascular injury. Experimental animals with the same intestinal ischemia–reperfusion injury but treated with anti-TNF antibody did not have an increase in lung permeability (0.36 ± 0.06); indeed there was no difference between these animals and the sham-operated group that had no intestinal injury. To eliminate the possibility that a rabbit heterophile antibody accounted for the observed protective effect, additional control animals were prepared using normal rabbit serum, as described above. The 120/120 control groups (normal rabbit serum) continued to show a significant ($p = 0.005$) microvascular permeability increase when compared to sham-treated and anti-TNF antibody-treated animals (data not shown).

Myeloperoxidase (MPO) Content of the Lung After Intestinal Ischemia–Reperfusion Injury and Treatment with Anti-TNF Antibody (Fig. 4)

Because of the possible relationship between TNF and neutrophils in the pathogenesis of this acute lung injury, neutrophil sequestration in the lungs following anti-TNF antibody treatment was assessed using the tissue myeloperoxidase assay described above. Previously we showed that significant pulmonary sequestration of neutrophils occurs following this intestinal ischemia–reperfusion injury.[6]

In a series of similar experiments with anti-TNF antibody treatment and normal serum controls, lung tissue MPO content was determined to assess pulmonary neutrophil sequestration. Sham-operated (0/0) animals given normal serum showed no difference in lung MPO content from animals given anti-TNF antibody (0.28 ± 0.07 *versus* 0.32 ± 0.07 U/g, respectively, $p > 0.05$). Similarly, in experimental animals with 120 minutes of intestinal ischemia and 120 minutes of reperfusion, there was no dif-

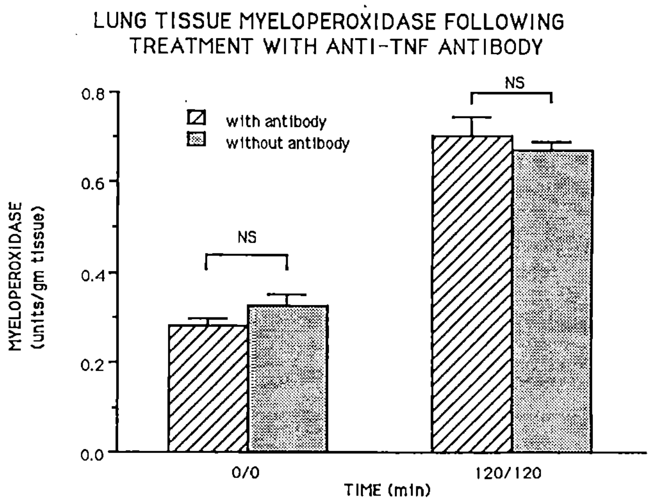

FIG. 4. Myeloperoxidase content of lungs in animals subjected to intestinal ischemia and reperfusion is not altered by treatment with anti-TNF antibody. Pulmonary neutrophil sequestration occurs despite the inhibition of TNF activity and the attenuation of the microvascular permeability increase. Time points on the x axis represent minutes of intestinal ischemia/minutes of intestinal reperfusion, (*e.g.*, 120/120 represents 120 minutes of ischemia and 120 minutes of reperfusion).

ference in lung MPO content between animals given anti-TNF antibody (0.63 ± 0.03) and those given normal serum (0.64 ± 0.09). Both anti-TNF antibody-treated and control serum-treated groups at 120/120 showed significant sequestration of neutrophils in the lungs compared to sham animals ($p < 0.05$). The dose of antibody that effectively prevented the microvascular permeability increase produced no reduction in pulmonary neutrophil sequestration.

Discussion

Tumor necrosis factor is a peptide of approximately 17 kd derived principally from stimulated macrophages. Although a number of other cytokines appear to be involved, TNF appears to be a proximal and critical mediator of the systemic inflammatory response to sepsis. Infusion of appropriate doses of recombinant human TNF in animals produces multiple-organ system injury, hypotension, and death in a pattern indistinguishable from endotoxemia.[11,22,23] In humans fever, tachycardia, hypotension, hypermetabolism, and increased whole-body lipolysis and fat use result from intravenous TNF administration.[23,24] Again the pattern mimics that of systemic sepsis.

Acute lung injury with neutrophil sequestration and increased microvascular permeability is characteristic of experimental animal models in which intravenous TNF is administered. These also are features of human ARDS. Tumor necrosis factor is thought to exert control in this process through the ability to activate the neutrophil. The result of neutrophil exposure to TNF includes increased superoxide anion generation,[25] increased neutrophil aggregation, and adherence to endothelial cells,[26] release of leukotriene B_4,[27] and enhanced phagocytosis.[28] Each of these effects is relevant to the process of neutrophil-mediated alveolar endothelial cell injury.

The acute lung injury described in these experiments after intestinal ischemia–reperfusion was associated with increased lung microvascular permeability, pulmonary neutrophil sequestration, and diminished lung tissue ATP levels.[6] The intestinal injury was associated with prompt release of endotoxin into the portal venous circulation (within 30 minutes of onset of ischemia). This was followed by release of significant quantities of TNF into the systemic circulation after 120 minutes of ischemia and reperfusion for 15 to 30 minutes. The observation that maximal TNF elevation occurred after a short period of intestinal reperfusion supports but does not prove the hypothesis that oxygen metabolites augment TNF release.[29] The appearance of TNF in systemic plasma 2 hours after initiation of gut injury is consistent with the suggestion that TNF is not stored in significant quantities in cytoplasmic granules, but stimulation is followed rapidly by transcription, translation, and then release, a series of processes measured in hours.[21]

Blocking the biologic effects of TNF is possible using monoclonal[30] or polyclonal anti-TNF antibodies[16] or by the induction of tolerance.[31] These experiments used a specific rabbit-derived polyclonal antiserum against murine TNF that cross-reacts with rat TNF.[16] The increase in microvascular permeability characteristic of the lung injury was reduced approximately 50% in animals pretreated with anti-TNF antibody (Fig. 3). The level of protection afforded was such that no statistical difference was present between sham-operated and experimental animals treated with the anti-TNF antibody. Importantly, however, the anti-TNF antibody did not prevent pulmonary neutrophil sequestration (Fig. 4). Stephens[11] and others[10,32] have suggested that neutrophils are the effector cells in TNF-mediated lung injury. These data suggest that the process of neutrophil sequestration occurs independent of TNF in this model. The observation that the microvascular lung injury was attenuated with the antibody to TNF suggests that the PMN activation process *in vivo* may, in part, depend upon TNF. Definition of the precise relationships between these mediators will require additional investigation.

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Blunt Traumatic Cardiac Rupture

A 5-Year Experience

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Blunt traumatic cardiac rupture is associated with a high rate of mortality. A review of the computerized trauma registry (1983 to 1988) identified 32 patients with this injury (ages 19 to 65 years; mean age, 39.5 years; 21 men and 11 women). Twenty-one patients (65.6%) were injured in vehicular crashes, 3 (9.4%) in pedestrian accidents, 3 (9.4%) in motorcycle accidents; 3 (9.4%) sustained crush injury; 1 (3.1%) was injured by a fall; and 1 (3.1%) was kicked in the chest by a horse. Anatomic injuries included right atrial rupture (13 [40.6%]), left atrial rupture (8 [25%]), right ventricular rupture (10 [31.3%]), left ventricular rupture (4 [12.5%]), and rupture of two cardiac chambers (3 [9.4%]). Diagnosis was made by thoracotomy in all 20 patients presenting in cardiac arrest. In the remaining 12 patients, the diagnosis was established in seven by emergency left anterolateral thoracotomy and in five by subxyphoid pericardial window. Seven of these 12 patients (58.3%) had clinical cardiac tamponade and significant upper torso cyanosis. The mean Injury Severity Score (ISS), Trauma Score (TS), and Glasgow Coma Scale (GCS) score were 33.8, 13.2, and 14.3, respectively, among survivors and 51.5, 8.3, and 7.0 for nonsurvivors. The overall mortality rate was 81.3% (26 of 32 patients), the only survivors being those presenting with vital signs (6 of 12 patients [50%]). All patients with rupture of two cardiac chambers or with ventricular rupture died. The mortality rate from myocardial rupture is very high. Rapid prehospital transportation, a high index of suspicion, and prompt surgical intervention contribute to survival in these patients.

CARDIAC RUPTURE AFTER blunt trauma is a relatively uncommon diagnosis; however it is associated with a very high mortality rate.[1] In 1955 DesForges reported the first successful repair of cardiac rupture after blunt trauma.[2] This opened a new era in the management of rupture of the heart because recognition of this injury was no longer purely academic. Since this initial success, multiple isolated accounts of repair of blunt cardiac ruptures have been reported.[3-14] Within the past decade, a few small series containing patients with blunt cardiac rupture have been recorded.[15-19] This present report reviews a 5-year experience with 32 patients who sustained cardiac rupture after blunt trauma and represents the largest series of treated patients with this entity reported to date.

Patient Data

During a 5-year period (beginning in 1983), 9522 patients who had sustained blunt trauma were admitted to the Shock Trauma Center of the Maryland Institute for Emergency Medical Services Systems (MIEMSS). An analysis of the MIEMSS trauma registry (prospectively collected data)[20] for the same period identified 32 patients with the diagnosis of blunt cardiac rupture. The mean age was 39.5 years, with a range from 19 to 65 years. There were 21 men and 11 women.

Twenty-one patients (65.6%) were injured in motor vehicle accidents (MVAs); three patients (9.4%) in auto–pedestrian accidents, and three in motorcycle accidents. Three sustained crush injury, one (3.1%) was injured by a fall, and one was kicked in the chest by a horse.

Twenty-eight patients were transported by helicopter and four by ground ambulance units. Thirty patients were admitted directly from the scene and two patients were transferred from local hospitals. The average time from injury to admission was 61.6 minutes.

The anatomic injuries included right atrial rupture (13 [40.6%]), left atrial rupture (8 [25%]), right ventricular rupture (10 [31.3%]), and left ventricular rupture (4 [12.5%]). Three patients (9.4%) had rupture of two cardiac chambers.

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Presentation

Twenty patients presented in cardiac arrest: 16 of them arresting at the scene and four during transport. Twelve patients had vital signs present at admission, and, of these, seven had systolic blood pressure less than 90 mmHg. Clinical evidence of cardiac tamponade (jugular venous distention, muffled heart sounds, and elevated central venous pressure) was noted in 7 of the 12 patients presenting with vital signs. These seven patients also were noted to have significant upper torso and facial cyanosis on admission. Two patients with associated pericardial lacerations presented with massive hemothorax and hemorrhagic shock. Visible external evidence of chest wall injury was noted in only 9 of the 32 patients.

Diagnosis

All 20 patients presenting in cardiac arrest underwent emergency thoracotomy in the admitting area, which established the diagnosis. Seven of the twelve patients who presented with vital signs had the diagnosis made by urgent left anterolateral thoracotomy, because of clinical deterioration. The remaining five patients underwent diagnostic subxyphoid pericardial window because of persistent hypotension or elevated CVP.

Associated thoracic injuries in the patients presenting with vital signs included multiple rib fractures (3), ruptured descending thoracic aorta (1), bilateral flail chest (1), ruptured superior vena cava (2), pericardial rupture (2), laceration of the pulmonary vein (1), and rupture of the inferior vena cava (2).

Treatment

Left anterolateral thoracotomy was performed in eight patients and median sternotomy in four patients of those presenting with vital signs. All 12 patients underwent primary repair of the injury without the assistance of cardiopulmonary bypass. Atrial injuries were primarily oversewn with 2-0 or 3-0 sutures, and ventricular injuries were repaired with deep pledgeted horizontal mattress sutures.

The 20 patients who presented in cardiac arrest all underwent immediate left anterolateral thoracotomy with attempted repair of the injury. Cardiopulmonary bypass also was not used in this group.

Morbidity/Mortality

The average Injury Severity Score (ISS) among all 32 patients was 49.7 (range, 29 to 75). The mean values for Trauma Score (TS) and Glasgow Coma Scale (GCS) were 5.4 and 6.0, respectively. The overall mortality rate was 81.3% (26 of 32 patients). None of the 20 patients presenting in cardiac arrest survived. For the 12 patients presenting with vital signs, the mortality rate was 50%. Among these 12 patients, the mean ISS, TS, and GCS were 33.8, 13.2, and 14.3, respectively, for survivors and 51.5, 8.3, and 7 for nonsurvivors. All three patients with injury to two cardiac chambers died. No patient with ventricular rupture survived.

Seven patients arrested in the admitting area; however only three (43%) of these subsequently died. The average length of stay of the six survivors was 27 days (range, 9 to 54 days). One additional patient survived operation but died of multiple-organ failure 11 days later.

Discussion

The treachery of blunt trauma is probably nowhere more evident than in the patient who presents to the hospital with blunt cardiac rupture. Because the incidence of this injury in patients presenting alive is very low, the diagnosis may not be entertained initially. Martin et al.[15] reported an incidence of only 0.5% among patients sustaining blunt trauma. Of 5378 trauma patients, 515 of whom sustained blunt chest trauma, Shorr et al.[21] noted 14 cases (0.3%) of cardiac lacerations. In the present study, the incidence was also 0.3% among blunt trauma victims. Observation of blunt cardiac rupture at autopsy, however, indicates that this injury indeed is not rare.[1,22]

The most common circumstance resulting in blunt rupture of the heart is an MVA. Of the 14 patients reported by Martin et al.,[15] eight had sustained their injuries in automobile accidents. Williams and coworkers also reported seven patients with blunt traumatic cardiac rupture, all of whom were involved in MVAs.[17] In the current report, 21 of the 32 patients were injured in MVAs. This was followed by auto–pedestrian accidents, falls from a height, and crush injury, which correlates with the literature.

The most compelling feature of cardiac rupture is cardiac tamponade. The patient may have multiple associated injuries that distort the clinical presentation. Hypotension out of proportion to identifiable blood loss should prompt cardiac tamponade as part of the differential diagnosis. Elevation of central venous pressure, jugular venous distention, and equalization of cardiac filling pressures also may suggest the diagnosis. Seventy-six per cent of patients surviving blunt cardiac rupture have been found to have significant upper torso, head, and neck cyanosis.[23] Of the 12 patients in our series who presented with vital signs, 7 had this finding documented. This is probably related to compression of the segment of the superior vena cava within the pericardium or compression of the vessels of the upper mediastinum from bleeding. Pericardiocentesis in cardiac trauma for purposes of diagnosis has been met with mixed reports in the literature, with high false-positive or false-negative results.[24–26] We have not found it to be a definitive test. Assuming that the patient is not in extremis, we prefer a subxyphoid diagnostic pericardial window performed in the operating room, with the patient fully prepared and draped for potential exploration.[27]

Besides cardiac tamponade, the other primary manifestation of cardiac rupture is exsanguinating hemorrhage with massive hemothorax. This usually occurs in the small percentage (approximately 10%) of patients who have an associated pericardial laceration. Mortality rate has been reported to be much higher in these patients because of earlier exsanguination due to loss of the tamponading effect of the intact pericardium.[28] In our series two patients had associated pericardial lacerations and neither survived.

Several etiologic mechanisms of blunt cardiac rupture have been postulated. Severe precordial impaction, with posterior compression of the sternum and anterior chest wall, leading to cardiac entrapment between the sternum and vertebral column, is one possible mechanism.[15] Both the atria and ventricles appear to be more vulnerable to compressive forces at points in the cardiac cycle of maximal filling.[22] Rapid deceleration with resultant disruption of the atria from their junctions with the vena cava and pulmonary veins is another reported theory.[15] Compression of the lower extremities and abdomen with rapid increase in intrathoracic hydrostatic pressure, due to upward displacement of blood, is another reputed mechanism.[1,22] In this instance the precipitous increase in venous pressure is transmitted directly to the atrium.

The anatomic locations of cardiac rupture in 40 survivors with 42 injuries from the literature were reported by Leavitt et al.[23] in a collective review. These were as follows: right atrium, 21 patients (50%); right ventricle, 7 (17%); left atrium, 10 (24%); and left ventricle, 4 (9%). Thus, among survivors, the right atrium and right ventricle were twice as likely to be injured as the left atrium and left ventricle, respectively. Of the six survivors in the present series, five had right atrial injuries and one had left atrial injury. No survivors had ventricular injury.

The surgical approach to the patient with cardiac rupture varies in the literature with proponents of either median sternotomy or left anterior thoracotomy. Leavitt et al. found an almost equal incidence in their review, with 48% median sternotomy and 45% left anterior thoracotomy.[23] We prefer the left anterior thoracotomy for the patient in extremis because of expedience and simplicity. The sternum is divided when necessary. For the more stable patient who has undergone subxyphoid window, the incision is extended to median sternotomy. This provides good exposure of the heart and ascending aorta, can be extended easily for laparotomy, and is suitable for cardiopulmonary bypass.

Once the site of rupture has been identified, surgical management of the lesion is essentially straightforward. Hemorrhage from atrial injuries may be controlled by direct compression or application of a vascular clamp. The injury can then be oversewn. Insertion of a Foley catheter through the wound, with inflation of the balloon and gentle traction, also has been found to be useful in controlling hemorrhage.[17,29] Ventricular injuries should be controlled by direct digital pressure and closure with mattress suture technique using pledget reinforcements.[17,30] Injuries in close proximity to the coronary arteries require placement of sutures beneath the vessels in horizontal mattress fashion.[16,29] Posterior lesions can be approached by temporary inflow occlusion for 1 to 2 minutes.[17,30] Intracardiac injuries should be managed electively after cardiac catheterization unless hemodynamic instability precludes postponing cardiopulmonary bypass.[16,31] After operation all patients definitely should be evaluated noninvasively for the possibility of occult septal and valvular injury.[18,32,33]

The mortality rate in patients with blunt traumatic cardiac rupture is extremely high. Shorr et al.[21] reported no survivors in 14 patients. Martin et al.[15] noted a 50% mortality rate and Mattox et al.[16] reported a mortality rate of 85%. The latter corresponds to our current reported mortality rate of 81.3%. For patients presenting with vital signs, the mortality rate in our group was 50%.

Some form of cardiac injury has been reported in 75% of traumatized patients, with blunt cardiac trauma accounting for at least 5% of the 50,000 highway deaths in the United States each year.[18] The diagnosis may be very difficult because many patients have associated injuries.[21,23] One must be mindful of the syndrome of cardiac tamponade in the patient with severe blunt chest trauma. If a patient arrests in the admitting area with a diagnosis of cardiac tamponade subsequent to blunt trauma, our data suggest a survival rate of more than 50% with immediate thoracotomy. With more sophisticated transportation facilities and prehospital care, more of these patients are being seen alive by emergency personnel. The survival rate can be increased only by a high index of suspicion, aggressive expeditious diagnostic evaluation, and prompt appropriate surgical management.

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Treatment of Patients with Aortic Dissection Presenting with Peripheral Vascular Complications

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The incidence of peripheral vascular complications in 272 patients with aortic dissection during a 25-year span was determined, as was outcome after a uniform, aggressive surgical approach directed at repair of the thoracic aorta. One hundred twenty-eight patients (47%) presented with acute type A dissection, 70 (26%) with chronic type A, 40 (15%) with acute type B, and 34 (12%) with chronic type B dissections. Eighty-five patients (31%) sustained one or more peripheral vascular complications: Seven (3%) had a stroke, nine (3%) had paraplegia, 66 (24%) sustained loss of a peripheral pulse, 22 (8%) had impaired renal perfusion, and 14 patients (5%) had compromised visceral perfusion. Following repair of the thoracic aorta, local peripheral vascular procedures were unnecessary in 92% of patients who presented with absence of a peripheral pulse. The operative mortality rate for all patients was 25% ± 3% (68 of 272 patients). For the subsets of individuals with paraplegia, loss of renal perfusion, and compromised visceral perfusion, the operative mortality rates (± 70% confidence limits) were high: 44% ± 17% (4 of 9 patients), 50% ± 11% (11 of 22 patients), and 43% ± 14% (6 of 14 patients), respectively. The mortality rates were lower for patients presenting with stroke (14% ± 14% [1 of 7 patients]) or loss of peripheral pulse (27% ± 6% [18 of 66 patients]). Multivariate analysis revealed that impaired renal perfusion was the only peripheral vascular complication that was a significant independent predictor of increased operative mortality risk ($p = 0.024$); earlier surgical referral (replacement of the appropriate section of the thoracic aorta) or more expeditious diagnosis followed by surgical renal artery revascularization after a thoracic procedure may represent the only way to improve outcome in this high-risk patient subset. Early, aggressive thoracic aortic repair (followed by aortic fenestration and/or abdominal exploration with or without direct visceral or renal vascular reconstruction when necessary) can save some patients with compromised visceral perfusion; however, once visceral infarction develops, the prognosis is also poor. Increased awareness of these devastating complications of aortic dissection and the availability of better diagnostic tools today may improve the survival rate for these patients in the future. The initial surgical procedure should include repair of the thoracic aorta in most patients.

THE MOST OPTIMAL therapeutic approach for patients with aortic dissection complicated by peripheral vascular problems (*e.g.*, stroke, paraplegia, limb ischemia, and renal or mesenteric ischemia or infarction) and the implications of these complications are not clearly established. In the presence of stroke, which is most commonly associated with acute type A (AcA) dissection, we proposed that emergent aortic repair be considered routinely,[1–3] while others advocate delaying surgical intervention until the patient's neurologic status is established.[4] If a patient presents with lower extremity, renal, or mesenteric ischemia, the recommended initial approach has varied from replacement of the thoracic aorta[1,5] to local surgical revascularization of the threatened limb or end organ followed by interval thoracic aortic repair (type A dissection) or intensive medical therapy alone (usually type B dissection).[6–8] Delaying definitive aortic repair by emphasizing local surgical treatment of peripheral vascular complications or emphasis on medical rather than surgical management, however, may not provide the best overall results.[1,9]

Therefore we assessed the incidence of peripheral vascular complications in patients with aortic dissection during a 25-year time span and their outcome after a uniform, aggressive surgical approach directed primarily at repair of the dissected thoracic aorta. Local surgical treatment of specific peripheral vascular complications was under-

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taken only if pathoanatomic deficits persisted after replacement of a segment of the thoracic aorta.

Methods

Definitions

Two hundred seventy-two consecutive, unselected patients underwent operation for spontaneous aortic dissection on the University Cardiovascular Surgical Services at Stanford University Medical Center between 1963 and 1987. No patient was denied operation because of age, complications, or moribund status; only brain death precluded operation.[10] The type of dissection was classified according to the Stanford nomenclature scheme proposed originally by Daily et al.[11] in 1970: dissections involving the ascending aorta (regardless of the site of primary intimal tear and extent of distal propagation of the dissecting hematoma) are type A; those without involvement of the ascending aorta are type B. The dissection was defined as acute if symptoms occurred less than 14 days earlier, and chronic if more than 14 days earlier.

Specific peripheral vascular complications, including stroke, paraplegia, peripheral pulse loss, and renal or visceral perfusion impairment, were diagnosed by retrospective review of history, physical examination, and angiographic reports (aortography was performed in more than 90% of patients). Location of pulse loss was categorized as carotid, upper extremity, or lower extremity deficits.

Statistical Analysis

Continuous data are expressed as mean ± 1 standard deviation (SD); clinically relevant ratios are presented with 70% confidence limits (CL) to indicate variability as applied to a larger population (*versus* the limited samples in this study). Statistical comparisons between categorical parameters were performed using chi-square analysis or Fisher's exact test; $p < 0.05$ was considered significant. Twenty-two specific preoperative factors were evaluated in terms of operative mortality: stroke, paraplegia, peripheral pulse loss, impaired angiographic renal perfusion, compromised angiographic visceral perfusion, aortic rupture, aortic valvular regurgitation, cardiac tamponade, shock, anuria, myocardial infarction, thromboembolism, renal dysfunction (serum creatinine level more than 1.5 mg/dL or blood urea nigrogen [BUN] more than more than 40 mg/dL), pulmonary disease (previously diagnosis or treatment for any chronic lung disorder), hypertension, operative date, age, sex, acuity (acute *vs.* chronic) and type (A *vs.* B) of dissection, tear location, emergency operation, and Marfan's syndrome. Operative death was defined as death occurring in hospital regardless of time after operation. Individual variables first were tested univariately (Duncan-Walker logistic regression analysis[12]); selected covariates that were significant ($p < 0.05$) or possibly significant ($p < 0.1$) then were tested using multivariate logistic regression analysis.[13] The relationships between the probability of hospital death (dependent variable) and the independent variables are described by the sign of the t statistic, a negative value implying an inverse relationship.

Patient Population

Patient age (196 male and 76 female) ranged from 14 to 86 years, with a mean of 57 ± 13 years. For the 21 patients (8%) with Marfan's syndrome, the average age was 39 ± 10 years. One hundred twenty-eight patients (47%) had acute type A (AcA) dissection, 70 patients (26%) had chronic type A dissection (ChA), 40 patients (15%) had acute type B dissection (AcB), and 34 patients (12%) had chronic type B dissection (ChB). The site of primary intimal tear was determined according to angiographic, surgical, or necropsy findings; the tear was located in the ascending aorta in 177 patients (65% ± 3%), the aortic arch in 34 patients (13% ± 2%), and the descending aorta in 61 patients (22% ± 3%).

Eighty-five patients (31%) sustained one or more peripheral vascular complications; of these, 18 patients (21%) suffered two complications, 6 patients (7%) had three complications, and 1 patient (0.4%) had four complications. Seven individuals (3%) presented with stroke, 9 (3%) with paraplegia, and 66 (24%) with loss of one or more peripheral pulses (Table 1). Twenty-two patients (8%) had compromised renal perfusion by angiography (right renal artery involved in 12 patients, left renal artery in 4, and bilateral renal artery involvement in 6), and 14 (5%) had compromised visceral perfusion by angiography. Table 2 summarizes other major (nonvascular) problems that further complicated the clinical presentation of these patients with peripheral vascular problems. The distribution of individual peripheral vascular complications according to dissection type is shown in Figure 1. The frequency of

TABLE 1. *Location of Absent Peripheral Pulses in 66 Patients**

Location	AcA	ChA	AcB	ChB	Total
Right carotid	6	0	0	1	7
Left carotid	6	0	0	0	6
Right arm	25	2	0	0	27
Left arm	10	1	2	0	13
Right leg	21	4	4	1	30
Left leg	14	0	3	1	18
Total	82	7	9	3	101

* Twenty-four patients had two or more pulse deficits.

AcA, acute type A; ChA, chronic type A; AcB, acute type B; ChB, chronic type B.

TABLE 2. *Other Major Complications in Patients Presenting with Peripheral Vascular Complications**

Complication	Stroke (n = 7)	Paraplegia (n = 9)	Pulse (n = 66)	Renal (n = 21)	Visceral (n = 14)
MI	0	0	1	1	0
Rupture	3	3	15	5	4
Cardiac tamponade	1	2	4	2	2
AI	4	2	17	6	5
Shock	1	2	3	2	3

* Some patients had more than one other preoperative complication. MI, myocardial infarction; AI, aortic valvular insufficiency.

'Pulse,' 'renal,' and 'visceral' imply loss or compromise of blood flow.

specific complications subdivided by acuity and type of dissection is illustrated in Figure 2.

Operative Techniques

Patients with type A aortic dissections were approached *via* a median sternotomy.[10] Using total cardiopulmonary bypass, the ascending aorta and the intimal tear (if exposed) were resected and replaced with a tubular woven Dacron graft. Aortic valvular insufficiency resulting from proximal extension of the dissecting hematoma was present in 84 of 198 patients (42%) with type A dissection; the aortic valve was resuspended or, less commonly, replaced. In seven patients, concomitant arch replacement was performed.

Patients with type B dissections underwent a left posterolateral thoracotomy. Using partial (femoral–femoral) cardiopulmonary bypass, a short segment of descending aorta containing the area of most severe injury (and the intimal tear, if exposed) was resected, followed by interposition of a tubular Dacron (E. I. Du Pont de Nemours and Co., Inc., Wilmington, DE) graft. In one patient with a limited acute arch dissection (type B), replacement of the transverse arch was performed through a median sternotomy using hypothermic circulatory arrest.

Concomitant local vascular procedures were necessary at the time of central thoracic aortic repair in 5 of 66 patients (8%) who presented with pulse deficits to relieve persistent distal ischemia: three required peripheral vascular reconstruction, and two (both AcA) abdominal aortic fenestration. One patient (AcA) required right carotid artery interposition grafting, one patient (ChA) with Marfan's syndrome underwent resection of an associated left subclavian aneurysm and external wrapping of a left femoral artery aneurysm, and one patient (ChA) received an innominate artery bypass graft for persistent innominate occlusion.

Two other patients who did not present with pulse deficits or limb ischemia required peripheral vascular procedures early after operation: One patient (ChB) developed lower extremity pulse loss and underwent right femoral embolectomy and femoral–femoral bypass grafting for left iliac artery occlusion; one patient (AcA) who developed right lower limb ischemia 4 days after operation (from extension of the dissecting hematoma into the right iliac artery) underwent fenestration of the abdominal aorta.

Adjunctive exploratory laparotomy for suspected visceral ischemia or infarction was performed in three individuals (representing only 21% ± 11% [3 of 14] of patients with angiographically documented compromised visceral perfusion). One patient underwent simultaneous small bowel resection at the time of central aortic repair. Two patients who developed abdominal pain and bloody diarrhea after operation underwent abdominal exploration; one required small bowel resection, and no gastrointestinal abnormalities were found in the other patient. In addition two other patients without preoperative angiographic evidence of visceral artery compromise underwent exploratory laparotomy after operation: one had no abnormalities and the other required small bowel resection. No local visceral or renal artery reconstructive surgical procedures were performed.

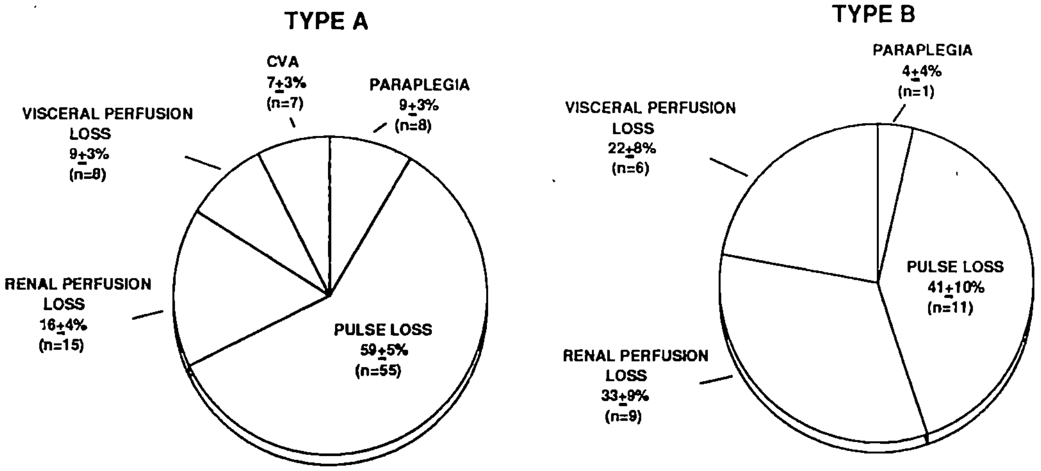

FIG. 1. Distribution of peripheral vascular complications (total = 120) according to type of dissection in the 85 patients who presented with one or more peripheral vascular problems. CVA, stroke.

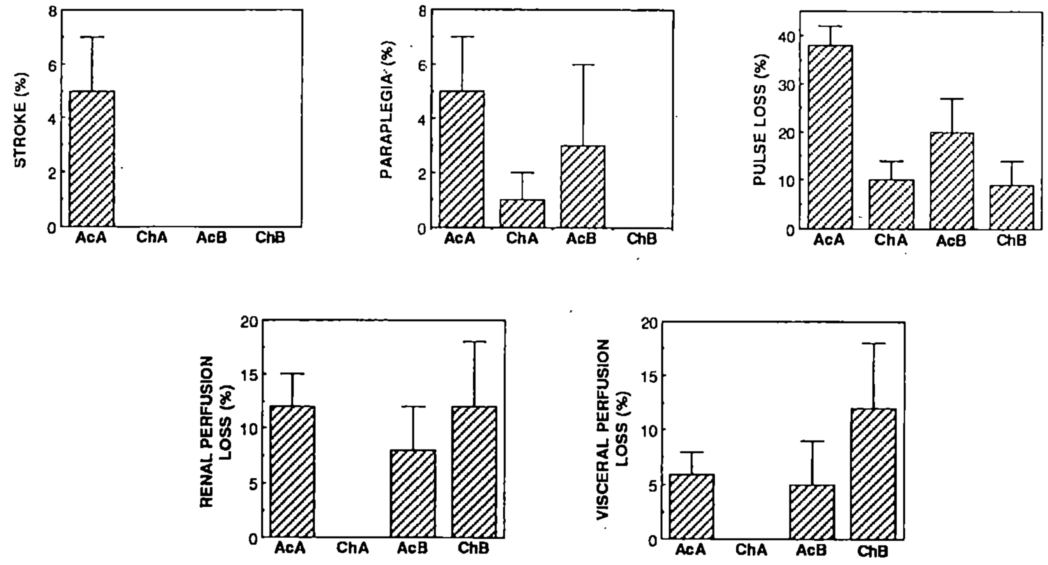

FIG. 2. Frequency of specific individual peripheral vascular complications subdivided according to acuity and type of aortic dissection. AcA, acute type A; ChA, chronic type A; AcB, acute type B; ChB, chronic type B.

Results

Overall Operative Mortality Rate

Sixty-eight of the two hundred seventy-two patients died, yielding an overall hospital mortality rate of 25% ± 3% during this 25-year period. The hospital mortality rate for patients with AcA dissections was 25% ± 4% (32 of 128 patients), which was not significantly different than 20% ± 5% for those with ChA dissections (14 of 70 patients; p = not significant [NS]). Patients with AcB dissections had a significantly higher operative mortality rate compared to those with ChB dissections (40% ± 8% [16 of 40 patients] *versus* 18% ± 7% [6 of 34 patients]; $p < 0.05$). The overall operative mortality rate for patients with peripheral vascular complications (28% ± 5% [24 of 85 patients]) was not significantly higher than that for patients without peripheral vascular complications (24% ± 3% [44 of 187 patients]; p = NS). The operative mortality rates for patients with and without peripheral vascular complications according to dissection acuity and type are listed in Table 3. In the AcB dissection subgroup, patients with peripheral vascular complications, had a significantly higher operative mortality rate than did those without vascular complications (64% ± 15% *versus* 31% ± 9%; $p < 0.02$). Table 4 summarizes the mortality rates for patients with each individual peripheral vascular complication according to acuity and type of dissection, as will now be described.

TABLE 3. *Summary of Operative Mortality Rates for Patients With and Without any Peripheral Vascular Complications*

Dissection Type	With	Without	p
AcA	24% ± 6% (15/61)	25% ± 6% (17/67)	NS
ChA	14% ± 14% (1/7)	21% ± 5% (13/63)	NS
AcB	64% ± 15% (7/11)	31% ± 9% (9/29)	<0.02
ChB	17% ± 16% (1/6)	18% ± 8% (5/28)	NS
Total	28% ± 5% (24/85)	24% ± 3% (44/187)	NS

NS, not significant.

Cerebrovascular Accident

Despite the compromised preoperative status of patients presenting with stroke, the operative mortality rate was relatively low (14% ± 14% [1 of 7 patients]); furthermore stroke was not a significant predictor of operative death (Table 5). One patient with a profound neurologic deficit died early after operation after being declared brain dead. The neurologic impairment persisted in one patient who required bypass grafting to the right common carotid artery at the time of ascending aortic replacement. One patient had extension of stroke and required a decompression craniotomy. Because of the irreversibility of the stroke, two patients with residual neurologic deficits died within 4 months of discharge.

Paraplegia

Among the nine patients presenting with paraplegia, four (44% ± 17%) died in the hospital (compared to 24% ± 3% [64 of 263 patients] for those without paraplegia); this complication, however, was not a significant predictor of operative mortality rate. Two patients died from myocardial infarction, and two due to respiratory insufficiency. Among the five operative survivors, one patient (ChA) developed paraparesis before operation secondary to rupture of the descending aorta; he underwent replacement of the entire thoracoabdominal aorta and thereafter had substantial resolution of his spinal cord injury. Another patient (AcA) underwent replacement of the ascending aorta, had gradual neurologic improvement after opera-

TABLE 4. *Summary of Operative Mortality Rates for Patients with Various Peripheral Vascular Complications According to Acuity and Type of Dissection*

	AcA		ChA		AcB		ChB	
Complication	N	OM	N	OM	N	OM	N	OM
Stroke	7	1 (14% ± 14%)	0	—	0	—	0	—
Paraplegia	7	3 (43% ± 19%)	1	0	1	1 (100%)	0	—
Pulse loss	48	12 (25% ± 6%)	7	1 (14% ± 14%)	8	4 (50% ± 18%)	3	1 (33% ± 28%)
Impaired renal perfusion	15	8 (53% ± 13%)	0	—	3	2 (67% ± 28%)	4	1 (25% ± 22%)
Compromised visceral perfusion	8	4 (50% ± 18%)	0	—	2	1 (50% ± 37%)	4	1 (25% ± 22%)

AcA, acute type A; ChA, chronic type A; AcB, acute type B; ChB, chronic type B. OM, operative deaths.

tion, and was able to ambulate with a cane after lengthy rehabilitation.

Peripheral Pulse Loss

The operative mortality rate for patients with aortic dissection presenting with pulse loss was 27% ± 6% (18 of 66 patients). Pulse loss, furthermore, was not a significant determinant of operative death. Causes of death in this subset included aortic rupture, myocardial infarction, sepsis and multiple-system failure, stroke, renal failure, respiratory insufficiency, technical problems, and coagulopathy. Importantly, of the 66 patients who presented with absence of peripheral pulses, only 5 (8%) required concomitant peripheral vascular procedures (vascular reconstructions in 3 and abdominal aortic fenestration in 2). Therefore 44 of the 48 operative survivors (92%) had spontaneous return of peripheral pulses and relief of limb ischemia after repair of the thoracic aorta.

One of the two other patients who required a peripheral vascular procedure after operation because of new postoperative limb ischemia died due to sepsis and multiple-organ failure.

Impaired Renal Perfusion

This complication was associated with a high operative mortality rate (50% ± 11% [11 of 22 patients]) compared to 23% ± 3% (57 of 250 patients) for those without compromised renal perfusion. Furthermore both impaired renal perfusion and renal dysfunction were significant independent predictors of operative death. Eight patients died in the immediate postoperative period; primary and secondary causes of death included aortic rupture, respiratory insufficiency, myocardial infarction, stroke, technical problems, gastrointestinal hemorrhage, and multiple-system organ failure. Three of eleven patients who died in hospital developed documented acute renal failure, one of whom required dialysis. Similarly 3 of 11 operative survivors developed acute renal failure, 2 of whom required dialysis (1 eventually recovered renal function).

Compromised Visceral Perfusion

The operative mortality rate for patients presenting with angiographically compromised visceral perfusion was also high—43% ± 14% (6 of 14 patients). This complication

TABLE 5. *Significant Univariate and Multivariate Determinants of Operative Death for all 272 Patients*

	Univariate		Multivariate		Operative Mortality	
Independent Variable	t	p	t	p	With (%)	Without (%)
Renal dysfunction	−3.88	0.0001	−3.71	0.002	50 ± 9	19 ± 3
Hypertension	−3.18	0.0015	−3.28	0.006	30 ± 4	14 ± 3
Impaired renal perfusion	−2.95	0.0032	−2.59	0.028	50 ± 11	23 ± 3
Age	2.86	0.0042	2.83	0.017		
Shock	−2.81	0.0049	NS	0.218		
Cardiac tamponade	−2.80	0.0052	−2.66	0.024	50 ± 12	21 ± 3
Anuria	−2.58	0.0010	NS	0.231		
Aortic rupture	−2.45	0.0145	NS	0.100		
Aortic regurgitation	2.36	0.0184	NS	0.103		
Operative date	−2.28	0.0225	−2.99	0.012		
Emergency operation	−1.84	0.0662	NS	0.234		
Pulmonary disease	−1.77	0.0769	NS	0.540		
Impaired visceral perfusion	−1.74	0.0827	NS	0.722		

NS, not significant ($p < 0.05$).

The operative mortality rates of patients with and without clinically relevant preoperative predictors are shown on the right.

per se, however, was not a significant, independent determinant of operative death (Table 5). For patients who required abdominal exploration, the operative mortality rate was even higher (80% ± 19% [4 of 5 patients]): one patient who underwent simultaneous bowel resection died during operation due to metabolic acidosis and myocardial failure, both patients who required postoperative bowel resection died in hospital (sudden death in one and renal failure in the other), and one of the two patients who were explored but did not need bowel resection died of respiratory insufficiency. Causes of death in the other patients included aortic rupture, renal failure, respiratory insufficiency, and technical problems.

Determinants of Operative Mortality: Multivariate Analysis

One (impaired renal perfusion) of the five peripheral vascular complications evaluated in this study emerged as a significant, independent predictor of operative death in the multivariate logistic analysis, as outlined in Table 5. Renal dysfunction, hypertension, older age, tamponade, and earlier operative date were the other significant, independent determinants portending a higher probability of operative death. In addition certain determinants, such as shock and aortic rupture, that appeared to be linked with higher risk on a univariate basis were not significant, independent risk factors in the multivariate analysis. Interestingly previous myocardial infarction, pulmonary disease, acuity and type of dissection, and site of intimal tear were not significant in either the univariate or the multivariate analyses.

Discussion

If untreated acute aortic dissection is associated with a mortality rate of 8% within the first 6 hours, 13% within 12 hours, 21% within 24 hours, and 74% in the first 2 weeks.[14] Causes of death in patients with untreated type A dissection include intrapericardial and free pleural rupture, aortic regurgitation, or, less commonly, compromised cerebral or coronary blood flow[14-18]; those with untreated type B dissection usually succumb to free pleural rupture or occlusion of major aortic tributaries resulting in injury to vital organs.[15,16] Thus the highly lethal nature of AcA and AcB aortic dissection mandates prompt and accurate diagnosis and early institution of definitive therapy.

While the dissecting hematoma may originate anywhere in the aorta, the most common location is in the ascending aorta.[14,16,19] In this study, 73% (198 of 272) of patients presented with type A dissection (47% [128 of 272] were acute); this figure is slightly higher than the approximately two-thirds incidence of type A dissection reported previously.[5,19-21] Type B dissection comprised 27% (74 of 272 patients) of this series, with the intimal tear generally located in the descending thoracic aorta. Rarely a type B dissection may originate in and propagate distally and proximally from an abdominal aortic tear.[14,22]

Although the most frequent presenting complaint is pain,[14-30] important, but less common symptoms reflecting acute peripheral vascular compromise may occur either due to extrinsic luminal compression by the dissecting hematoma in the false lumen or an intimal flap compromising the orifice of a branch artery.[5,6,14,24,26] In this series 31% of patients had one or more of five peripheral vascular complications (stroke, paraplegia, pulse loss, or impaired renal or visceral perfusion); this figure is similar to the 30% to 50% incidence of peripheral vascular complications reported previously.[6,21,24,26,28,31] Thus abrupt arterial occlusion in conjunction with an acute generalized illness involving unrelated organ systems should prompt strong consideration of the diagnosis of acute aortic dissection.

The most optimal treatment for patients with AcA dissections is emergency replacement of the ascending aorta in all cases.[4,5,16-18,24,25,27,31-37] The most optimal management of patients with uncomplicated AcB dissections, on the other hand, is less well standardized; intensive medical therapy alone generally is advocated for patients with AcB dissections,[16,36,38] whereas surgery is indicated if progression of the dissection, impending rupture, refractory hypertension, a sizable localized false aneurysmal component, or continued pain are present.[16,37] We postulated that the long-term outcome might be better if a more aggressive early surgical approach for selected patients with AcB dissections were carried out before the development of life-threatening complications,[2,5] but a combined study from Duke and Stanford recently documented that long-term outcome actually was similar after either medical or surgical treatment.[39]

The most optimal treatment strategy remains to be defined for patients with aortic dissection complicated by peripheral vascular problems. While some investigators recommend that surgical treatment initially be directed toward the peripheral vascular complication (such as mesenteric, renal, or lower extremity ischemia),[6] we repair the thoracic aorta first. Peripheral revascularization procedures or aortic fenestration were performed subsequently if end-organ ischemia persisted or developed thereafter. These are vexing complications associated with high mortality rates, however, and more information regarding these questions is needed.

Cerebrovascular Accident

Central and peripheral nervous system deficits can complicate the clinical picture in up to one third of patients with type A dissection.[16,26,28,31,40-42] Depending on the specific pathologic anatomy, syndromes related to central nervous system involvement may vary from syncope to focal neurologic signs to frank coma; peripheral nervous system involvement may be manifested as ischemic peripheral neuropathy or paraplegia.[40,43] Stroke occurs infrequently, with an incidence of 3% (5% of AcA subset) in this study and 6% to 7% in others.[6,21,26,28,30,44] Because the combination of heparinization and restoration of cerebral perfusion may precipitate hemorrhage and extension of cerebral infarction, stroke has been considered to be a contraindication to emergency surgery in patients with acute dissection[4,6]; therefore it has been advocated that medical management be used until the neurologic situation stabilizes.[4] Our experience in patients with stroke revealed that an aggressive surgical approach (replacing the ascending aorta and obliterating the distal false lumen) was associated with an operative survival rate of 86% ± 14% (6 of 7 patients); furthermore stroke was not a significant predictor of operative death. Extension of the stroke occurred in two patients. The irreversible nature of the cerebral injury in some patients, however, limits long-term survival.[2,10] Nonetheless, as reflected by a favorable outcome in four patients (57% ± 19%), stroke probably should constitute only a relative contraindication to central aortic repair.

Paraplegia

Spinal cord injury can be a key diagnostic clue in patients with acute aortic dissection.[45] In this study the incidence of paraplegia complicating aortic dissection was 3% (compared to a range of less than 2% to 6% in previous reports[6,21,30,46]): most patients had extensive AcA dissections. Our approach in such cases was not modified by the presence of paraplegia, although the operative mortality rate was high (44% ± 17%). Paraplegia *per se*, however, was not a significant risk factor for operative death, perhaps due to the very small number of patients with this devastating complication. After operation there was only a small possibility of neurologic improvement,[6,47] a fact that must be understood clearly by the patient, the patient's family, and all involved physicians. We believe that urgent operative intervention should still be considered in patients with aortic dissection complicated by paraplegia to prevent other lethal complications.

Pulse Deficits and Limb Ischemia

Although the usual differential diagnosis of spontaneous acute limb ischemia includes arterial embolization and thrombosis due to pre-existing atherosclerosis, aortic dissection also should be considered.[1,7,8,48–52] It has been reported that pulse loss occurs in as many as one half of patients with type A dissection[26] and one quarter of all patients.[6,27] In this analysis most peripheral pulse deficits occurred in patients with AcA dissections, probably because of the frequency and extensive nature of this lesion (Table 2); 38% of patients with AcA dissections and 24% of all patients had peripheral pulse deficits. Pulses in the right arm and right leg were affected most often. Other researchers[6] have noted that these peripheral pulse deficits may resolve spontaneously in up to one third of patients, presumably due to redirection of flow into the true lumen or spontaneous fenestration of the aortic false lumen. After aortic repair our findings indicated that a many patients (92% ± 3%) had restoration of peripheral pulses and relief of limb ischemia without the need for additional peripheral revascularization procedures. In a few instances, it was necessary to perform aortic fenestration or a separate peripheral bypass procedure to alleviate persistent peripheral ischemia.

We concur that in patients with leg ischemia, factors related to the proximal aorta (*i.e.*, type of dissection and general operative risk) should dictate the mode of treatment because of the lethal nature of AcA aortic dissection.[5] Local peripheral vascular operations (*e.g.*, femoral–femoral bypass grafting) generally are inappropriate because often they are unnecessary after direct (central) thoracic aortic repair and, most importantly, can delay definitive surgical treatment, which can lead to a disproportionately high death rate. In addition peripheral pulse loss was not a significant risk factor for operative death. We believe that definitive repair of the thoracic aorta should take priority.

Impaired Renal Perfusion

Because dissection and/or occlusion of the renal arteries can result in renal ischemia or infarction,[26] the presence of renal symptoms, such as oliguria, flank pain, and hematuria, are of diagnostic and prognostic importance.[32,53,54] Previously it was noted that the left renal artery is more frequently affected than the right, probably because the more anterior right renal artery orifice is involved only if there is considerable circumferential extension of the dissection.[55] In this study, on the other hand, the left renal artery was involved less often than the right. Also, while some have reported that the incidence of renal artery involvement ranges from 12% to 60% in patients with aortic dissection,[14,55–57] we and others have observed a lower incidence, *e.g.*, 8% in this study and 5% reported previously.[6] These differences probably reflect the method of detection (angiography *versus* autopsy) rather than true population differences.[6] Although others have performed local renal artery revascularization procedures during the acute phase,[6,58] this approach is rarely successful (in the presence of deteriorating renal function, the mortality rate was 50% in one study).[6] The philosophy of our group and others[54] has been to replace the diseased thoracic aorta because this eliminates the most common causes of death and can potentially restore renal perfusion. Nevertheless the operative mortality rate in this subset of patients remains high in our experience (50% ± 11%), perhaps due to the moribund preoperative status of these patients and/

or long delays in making the correct diagnosis after repair of the thoracic aorta. More rigorous immediate postoperative surveillance (including liberal and aggressive use of ^{99}Technetium renal scans or angiography) may detect compromised renal perfusion earlier after thoracic aortic repair, which then should be approached with a local revascularization procedure or suprarenal abdominal aortic fenestration. Because loss of renal perfusion and renal dysfunction were significant independent predictors of operative death, it may be that the only way to reduce this risk is to intervene earlier before such develops,[5] although this may not be a realistic goal in all cases.

Compromised Visceral Perfusion

Fortunately acute dissection leading to mesenteric ischemia or infarction is uncommon ($\leq$ 3% reported previously,[6,21,59] 5% incidence in this study). The operative mortality rate for patients with this complication has been reported to be as high as 88%[6]; notwithstanding successful (local) visceral vascular reconstruction procedures, death often resulted from the sequelae of mesenteric infarction.[6] This experience prompted Cambria et al.[6] to advocate local surgical treatment of visceral ischemia initially followed by medical treatment in patients with type B dissection or interval (within days) ascending aortic repair in patients with type A dissection. In our experience with the initial operative approach focused on the thoracic aorta, the operative mortality rate for 14 patients with compromised visceral perfusion was 43% ± 14%, but this complication *per se* did not emerge as a significant, independent predictor of increased operative mortality risk in the multivariate analysis. While this mortality rate appears to compare favorably with that reported by Cambria et al.,[6] such may only reflect the fact that our patients simply had angiographic evidence of compromised visceral perfusion *versus* frank bowel ischemia or infarction in the Yale/MGH study.[6] Nevertheless we continue to believe that an early, aggressive surgical approach focused primarily on the thoracic aorta (followed by secondary supraceliac aortic fenestration, superior mesenteric artery revascularization, and/or bowel resection, when indicated) is the most prudent option for most of these extremely ill patients. It is clear, however, that once small bowel or colon infarction occurs, the overall survival rate will be disappointingly low, regardless of the surgical tactics used. For extremely high risk patients with AcB dissections in which a thoracotomy is judged to carry a prohibitive risk (on the basis of coexistent cardiac or severe pulmonary disease or advanced age) who also have visceral ischemia, we agree with Cambria and colleagues[6] that it may be preferable to attempt to restore visceral (and/or renal) blood flow initially. This can be performed using either innovative interventional radiologic catheter techniques (balloon dilatation and/or intimal flap 'septostomy') or a local surgical revascularization procedure *via* a retroperitoneal approach.

Interestingly we did not find shock, aortic rupture, acuity and type of dissection, site of intimal tear, myocardial infarction, pulmonary disease, acuity or type of dissection, and intimal tear location to be significant, independent determinants of operative death in the multivariate analysis. These factors previously have been observed by ourselves and others to portend poor operative outcome,[5] particularly shock and rupture.[5,6] Therefore consideration of prompt and definitive surgical treatment should not be excluded arbitrarily in such patients.

Certain limitations in this study should be addressed. This is a retrospective analysis of patients who presented with aortic dissection and underwent repair of the thoracic aorta. No patients were treated initially with local revascularization followed by definitive thoracic aortic repair, so we cannot comment directly about the effectiveness of such an approach. In addition the incidence of some complications, *e.g.*, paraplegia, stroke, or visceral infarction, may have been too low to allow them to attain statistical significance in the multivariate analysis; therefore it is possible that one or more of these devastating complications could portend increased operative mortality risk.

Conclusion

Thirty-one per cent of patients with aortic dissection had one or more acute peripheral vascular complications. Aortic dissection should be considered early in the differential diagnosis of individuals with acute pulse loss and renal, visceral, or cerebral ischemia. Following repair of the thoracic aorta, the outcome was relatively satisfactory in patients with stroke and peripheral pulse deficits, but was less favorable in those with paraplegia, impaired visceral perfusion, or compromised renal perfusion (the only peripheral vascular complication that was a significant, independent predictor of operative death). We believe that definitive treatment of the life-threatening underlying disease, *i.e.*, surgical repair of the thoracic aorta, should take priority; such will obviate the need for most peripheral revascularization procedures. Earlier diagnosis and operation for patients with compromised renal and/or visceral perfusion is still needed to minimize the occurrence of these frequently lethal complications.

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The Risk of Large Bowel Cancer After Partial Gastrectomy for Benign Ulcer Disease

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The relative risk (standardized incidence ratio [SIR]) for colorectal cancer after partial gastrectomy for ulcer disease was examined in a population-based cohort comprising 6459 patients operated during 1950 to 1958. Follow-up through 1983 revealed 131 cases of colorectal cancer *versus* 150.3 expected cases (SIR = 0.87; 95% confidence limits 0.73, 1.03). The relative risk was decreased during the first 19 years of follow-up (SIR = 0.75; 0.58, 0.96) and close to equal thereafter (SIR = 1.02; 0.79, 1.29). Sex, age at operation, type of operation, and diagnosis at operation (stomach or duodenal ulcer) did not affect the relative risk significantly. Confounding by socioeconomic status is one conceivable explanation for the decreased relative risk during the first years of follow-up, whereas the increasing risk with longer duration of follow-up might be a consequence of the surgical procedure itself.

COLORECTAL CANCER IS the second most common malignant neoplasm in developed countries.[1] Environmental influences have been considered important in the etiology of colorectal cancer because of lower incidence rates in Africa, Asia, and South America, and changing incidence rates over time and in migrating populations.[2] In Sweden the incidence has increased 0.5% to 1.1% annually since the establishment of the Swedish Cancer Registry in 1958.[3]

During recent years several reports have shown an increased risk for colorectal cancer after surgery for benign ulcer disease,[4–7] whereas other studies have shown an unchanged[8,9] as well as a decreased risk[10] (Table 1). Some authors suggest that any excess risk might be due to factors that cause the ulcer diathesis itself, such as cigarette smoking.[4,5] Other explanations would be that the surgical procedure is responsible by (1) leading to changes in eating habits, (2) altering the bacterial flora in the stomach so that bile acids are broken down to metabolites that promote carcinogenesis in the large bowel,[6] or (3) promoting endogenously formed N-nitroso compounds in the hypoacid gastric remnant.[11] Changes in the level of gastrin in the serum following gastric surgery also may affect the risk of developing large bowel cancer.[12–14]

Small numbers, short follow-up, and the use of mortality rather than incidence as an endpoint in these studies have hampered our ability to conclude definitely that surgery for ulcer disease is a determinant of large bowel cancer.[4–10] To further examine this hypothesis, we used data from a cohort study that showed an increasing risk of stomach cancer after partial gastrectomy[15] to report the incidence of colorectal cancer subsequent to partial gastrectomy in a cohort of 6459 patients followed for 25 to 33 years.

Methods

The subjects and methods of this study were described in detail recently.[15] The study was approved by the Swedish Data Inspection Board.

The Cohort

The source population consisted of residents in five countries within the Uppsala health care region with a total population of about 1.2 million in 1955. There were 20 surgical departments in this area during the 1950s. One of us (G.L.) visited these departments and searched the surgical records to identify all patients who had un-

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TABLE 1. *Published Retrospective Cohort Studies of Colon Cancer After Surgery for Benign Peptic Ulcer Disease*

Author	Year	No. of Patients	Observed Cases	Expected Cases	Observed/ Expected Ratio	95% Confidence Limits	Years of Follow-up	Endpoint
Ross et al.[4]	1982	779	16	8.9	1.80	1.03, 2.92	15–33	Mortality
Inokuchi et al.[7]	1984	3827	28	16.37	1.71	1.14, 2.47	10–33	Mortality
Watt et al.[5]	1984	735	12	5.2	2.31	1.19, 4.03	15–26	Mortality
Caygill et al.[8]	1987	4514	57	66.0	0.86	0.65, 1.12	25–45	Incidence
Toftgaard[9]	1987	3919	84	85.9	0.98	0.78, 1.21	22–28	Incidence
Thiruvengordam et al.[10]	1988	337	4	11.2	0.36	0.10, 0.91	20*	Incidence

* Median.

dergone partial gastrectomy for ulcer disease from 1950 to 1958. We excluded 679 patients because of a missing or an incorrect national registration number or death during the first postoperative year. After these exclusions 6459 patients (90% of all operated patients in the study population) remained in the final cohort.

The proportion of men to women in the cohort was 5:1. One half of the patients were younger than 50 years at the time of operation, and the age distributions of men and women were similar. The Billroth I procedure was performed in 1738 patients (27%), while 4693 patients (73%) were treated with the Billroth II procedure, and 28 patients underwent unknown procedures. At the time of operation 1755 patients (27%) had a diagnosis of stomach ulcer, 3947 (61%) duodenal ulcer, and 757 (12%) had an ulcer whose location was not stated. The classification of ulcer was based on the judgment of the surgeon and was the diagnosis reported in the surgical theater records.

Observed cases of colorectal cancer in the cohort, diagnosed after partial gastrectomy, were identified through computerized linkage to the National Cancer Registry. We examined the standardized incidence rations (SIR) of colon cancer (right sided, left sided, and all locations) and rectal cancer separately in relation to the various potential determinants shown in Table 2. The relative risk was similar for subsequent colon cancer (SIR = 0.85, 95% confidence limits [CL] 0.67, 1.06) and for rectal cancer (SIR = 0.90, 95% CL 0.67, 1.18). Within the former group the relative risk was only slightly lower for cancer on the right side of colon (SIR = 0.83, 95% CL 0.57, 1.16) than for that on the left side (SIR = 0.95, 95% CL 0.66, 1.32). Because the results did not differ significantly in different

TABLE 2. *Risk of Colorectal Cancer After Partial Gastrectomy by Site, Sex, Surgical Procedure, Diagnosis at Operation, Age at Operation, or Duration After Operation*

Variable	Observed Cases	Person Years	Expected Cases	SIR*	95% CL*
All patients	131	128,489	150.3	0.87	0.73, 1.03
Sex					
Male	111	101,764	120.2	0.92	0.76, 1.11
Female	20	26,725	30.1	0.66	0.41, 1.03
Surgical procedure					
Billroth I	41	34,053	39.4	1.04	0.75, 1.41
Billroth II	90	93,911	110.3	0.82	0.66, 1.00
Diagnosis at operation					
Stomach ulcer	32	30,952	44.3	0.72	0.49, 1.02
Duodenal ulcer	83	82,524	88.2	0.94	0.75, 1.17
Unknown	16	15,013	17.8	0.90	0.52, 1.46
Age at operation (years)					
<40	13	38,210	13.5	0.96	0.51, 1.64
40–49	31	41,116	39.4	0.79	0.53, 1.12
50–59	52	33,671	57.6	0.90	0.67, 1.18
60+	35	15,492	39.7	0.88	0.61, 1.23
Duration after operation (years)					
0–4	4	12,135	6.4	0.62	0.17, 1.60
5–9	14	27,064	18.5	0.76	0.41, 1.27
10–14	15	27,827	26.6	0.56	0.32, 0.93
15–19	30	24,931	32.1	0.93	0.63, 1.33
20–24	34	21,046	34.7	0.98	0.68, 1.37
25–29	27	12,867	25.9	1.04	0.69, 1.52
30+	7	2619	6.0	1.17	0.47, 2.41

* SIR, Standardized incidence ratio; 95% CL, 95% confidence limits of the standardized incidence ratio.

sites, all colorectal cancers have been combined as one single outcome in the following analyses. Histopathologic examination was the basis for colon cancer diagnoses in 92.5% of the cases; the diagnosis for the remaining cases depended on medical examination, x-ray, operation, or autopsy without morphologic confirmation. At the time of this study, cancer registration at the Cancer Registry had been completed until December 31, 1983 (the closing date), giving a follow-up period of 25 to 33 years.

Statistical Measures and Methods

The computation of person-years at risk started in 1958, the first year available for follow-up in the Swedish Cancer Registry. Each cohort member was followed to the date of colorectal cancer, the date of death, the date of emigration, or the closing date of this study. Person-years at risk of developing a colorectal cancer were calculated by 5-year age groups and sex during each year of observation. Patients operated on between 1950 and 1957 were not followed-up for the occurrence of colorectal cancer before 1958. During this period the patients will not contribute either with person-years or observed cases. If colorectal cancer developed in a patient after operation but before January 1, 1958, the patient would have contributed person-years at risk only if the patient had survived after 1958. The low prevalence[16] and incidence[3] of colorectal cancer at the age when most of the cohort members were operated on imply that such patients make a small contribution to estimated numbers of person-years at risk and have a negligible effect on the SIR.

Official statistics[3] from the Swedish Cancer Registry contained annual sex- and age-specific incidence rates for colorectal cancer. Multiplication of person-years for different 5-year age groups by sex and for successive years of observation by the corresponding age-specific incidence rates yielded the expected number of incident colorectal cancer cases in the cohort.

The SIR was defined as the ratio of observed numbers of stomach cancer to expected numbers. The 95% CL of the standardized incidence ratio then were calculated on the assumption that the observed number of cases in each group follows a Poisson distribution.[17] We analyzed the cohort by years after operation, sex, surgical procedure, diagnosis at operation, and age at operation. For further analyses, in which each subgroup is judged independently of others, we used Poisson regression analysis.[18]

Results

Univariate Analyses

A total of 131 colorectal carcinomas was diagnosed during the follow-up period 1958 to 1983, 13% less than the expected (SIR = 0.87; 95% CL 0.73, 1.03) (Table 2). No factors examined were statistically significant, but several findings were worth noting, especially for the multivariate analysis. Male patients had an 8% lower risk (SIR = 0.92, 95% CL 0.76, 1.11), and female patients a 34% lower risk (SIR = 0.66, 95% CL 0.41, 1.03) relative to that which was expected (Table 2). Patients operated on with the Billroth II procedure had a decreased relative risk (SIR = 0.82, 95% CL 0.66, 1.00); the relative risk after the Billroth I procedure was close to equal (SIR = 1.04, 95% CL 0.75, 1.11). Patients operated on for stomach ulcer had a 28% decreased relative risk (SIR = 0.72, 95% CL 0.49, 1.02), but those with duodenal ulcers had an unchanged relative risk (SIR = 0.94, 95% CL 0.75, 1.17). Age at operation was seemingly unrelated to the relative risk for subsequent colorectal cancer. A slightly but regularly increasing relative risk for colorectal cancer was, however, found during the follow-up period (Table 2).

Stratified Analyses

The increasing relative risks with increasing duration of follow-up seen in Table 2 are likely to reflect a continuous phenomena. However, because 5-year categories are too small for stratified analyses, a dichotomous grouping with a 20-year cutoff was chosen in accordance with another study[8] (Table 3). During the first period, 1 to 19 years after operation, the overall relative risk was 25% less than expected (SIR = 0.75, 95% CL 0.58, 0.96); and patients operated on with the Billroth II procedure had a 31% decreased relative risk (SIR = 0.69, 95% CL 0.50, 0.94). After 20 years the risk was close to that expected in the entire cohort (SIR = 1.02, 95% CL 0.78, 1.07) as well as in different subgroups (Table 3).

Multivariate Analyses

In the univariate analyses gender, surgical procedure, diagnosis at operation, and duration after operation slightly affected the risk of colorectal cancer. To study the joint effects of these four characteristics, we excluded the 27 patients operated on with unknown surgical procedure and grouped preoperative diagnosis in gastric ulcer, duodenal ulcer, and unknown. When added to a baseline Poisson regression model that assumed a constant standardized incidence ratio (131 observed cases/149.67 expected cases = 0.87), the only determinant that significantly improved the fit of the baseline model was duration of follow-up after operation (change in deviance = 4.08 with one degree of freedom; $p = 0.04$). Addition of age at operation did not improve the model fit or alter the risk estimates. The risk increased about 12% for each additional 5 years of follow-up (adjusted standardized incidence ratio = 1.12, 95% CL 1.00, 1.26).

TABLE 3. *Risk of Colorectal Cancer After Partial Gastrectomy, According to Duration of Follow-up After Operation and Several Other Characteristics of the Patients*

	0 to 19 Years After Operation					20 to 33 Years After Operation				
Variable	Observed Cases	Person Years	Expected Cases	SIR*	95% CL*	Observed Cases	Person Years	Expected Cases	SIR*	95% CL*
All patients	63	91,957	83.7	0.75	0.58, 0.96	68	36,532	66.6	1.02	0.79, 1.29
Sex										
Male	50	72,854	66.5	0.75	0.56, 0.99	61	28,910	53.7	1.14	0.87, 1.46
Female	13	19,103	17.2	0.76	0.40, 1.30	7	7622	12.9	0.54	0.22, 1.12
Surgical procedure										
Billroth I	21	24,864	22.8	0.92	0.57, 1.41	20	9189	16.6	1.21	0.74, 1.87
Billroth II	42	66,686	60.4	0.69	0.50, 0.94	48	27,225	49.9	0.96	0.71, 1.28
Diagnosis at operation										
Duodenal ulcer	37	57,207	45.2	0.82	0.58, 1.13	46	25,317	42.9	1.07	0.78, 1.43
Stomach ulcer	19	23,029	27.0	0.70	0.42, 1.10	13	7923	17.3	0.75	0.40, 1.28
Unknown	7	11,721	11.4	0.61	0.25, 1.26	9	3292	6.3	1.42	0.65, 2.70
Age at operation (years)										
>40	5	24,901	4.3	1.15	0.37, 2.68	2	13,309	9.2	0.87	0.37, 1.71
40–49	11	28,183	15.8	0.69	0.35, 1.24	20	12,933	23.6	0.85	0.51, 1.31
50–59	23	25,324	31.6	0.75	0.48, 1.12	29	8347	26.0	1.12	0.75, 1.60
60+	24	13,549	31.8	0.75	0.48, 1.12	11	1943	7.9	1.39	0.70, 2.49

* SIR, Standardized incidence ratio; 95% CL, 95% confidence limits.

Discussion

This study examined a cohort of 6459 patients, with complete follow-up during 128,489 person-years of observation, and found a borderline significant decreased relative risk for colorectal cancer after a partial gastrectomy for ulcer. Based on a Poisson distribution and a two-tailed test (alpha = 0.05), we had a power of 80% to detect a relative risk (SIR) of colorectal cancer lower than 0.8 or higher than 1.2 in the overall analysis. The decreased relative risk was virtually confined to the first 19 years after operation and was most pronounced among patients operated on with the Billroth II procedure. The risk relative to the expected increased for each additional 5 years of follow-up, indicating that this change in risk is a continuous phenomena. This finding in relation to duration after operation parallels that found in the stomach cancer study.[15]

Our results were based on a cohort compiled from the entire population in a well-defined geographic area. The organization of the Swedish public health system implies that virtually all patients in this area operated on for benign gastric or duodenal ulcer disease from 1950 through 1958 were included. Selection bias is thus limited to the patients not available for follow-up. Among all admissible patients, 384 could not be traced, probably because of erroneous addresses at the time of operation or from incomplete names. Another 122 patients had an erroneous national registration number—probably due to a transcription error occurring since operation—which is not unexpected in this large cohort of patients treated so long ago. There is no reason to believe that patients lost to follow-up differ from those retained in the cohort with respect to the risk of developing large bowel cancer.

The follow-up for the occurrence of colorectal cancer in this cohort was through the Swedish Cancer Registry, the same source used to calculate the expected cancer incidence rates. As a result, the slight underreporting of incident cancer to the Cancer Registry would have influenced both the observed and the expected numbers to the same extent. Incidence rates of colorectal cancer are only slightly unequally distributed among different geographic areas in Sweden.[19] In 1983 the age-standardized rate was 5% lower in the Uppsala health care region than that in the whole country,[3] which means that the SIRs in this study may be somewhat underestimated.

Some previous reports, both from case-control and from retrospective cohort mortality studies, have shown an elevated[4–7] overall risk for subsequent colorectal cancer after surgery for benign ulcer disease (Table 1). Bundred et al.[6] reported a 2.1 times increased risk in a case-control study with cases and controls from one hospital. There was no difference in the prevalence of peptic ulcer disease between the two groups. Ross et al.[4] followed 779 men operated on with gastrectomy or vagotomy for peptic ulcer and found an 1.8 times increased risk for colorectal cancer. Similar data emerged from a larger cohort study of Inokuchi et al.[7] In a follow-up study of 735 patients who underwent elective vagotomy and drainage procedures, Watt et al.[5] showed a ratio of observed to expected deaths in colorectal cancer of 2.3. Caygill et al.[8] followed a cohort of 4514 patients operated on with gastrectomy or vagotomy and found a 1.6 times excess risk for death due to colorectal cancer 20 years or more after operation, although there was a decreased number of deaths from colorectal cancer during the first 19 postoperative years and no overall increased risk (Table 1). Patients in these hospital-based mortality studies might have had closer follow-up (*e.g.*, more autopsies) than patients in the comparison populations, leading to the increased overall risks observed.

Other population-based incidence studies less susceptible to this problem have shown different overall results, more like those of our study. Toftgaard[9] studied a population-based cohort of patients with a gastrectomy or simple perforation suture; the relative risk for subsequent colorectal cancer was close to equal (Table 1). Thiruvengadam et al.,[10] on the other hand, found a significantly decreased relative risk of 0.4 in a population-based cohort. The number of observed cases was too small (only four), however, to account for duration of follow-up as a possible determinant of risk.

In accordance with some previous reports,[8,10] we found a decreased relative risk for subsequent colorectal cancer during the first 19 postoperative years. The effects of a potential confounder acting at and soon after the operation would more likely account for this early decreased risk than the operation itself because cancer is thought to develop many years after its cause (for example, the operation) has occurred. Socioeconomic status (SES) might act to decrease the incidence of colon cancer in this cohort because peptic ulcer disease is more common in Uppsala among those with lower SES,[20] whereas colorectal cancer is less common among those with lower SES.[2,21] We could not address SES directly in this study. SES, however, provides no explanation to the rising risk with increasing duration of follow-up.

The increasing risk of colorectal cancer after partial gastrectomy might be due to a change in eating habits, biochemical changes in the stomach, or changes in gastrin levels. After partial gastrectomy, eating habits may change, either because of the disappearance of ulcer symptoms or because of sequelae after operation.[22,23]

For instance intolerance of milk and milk foods was found in 47% of all postoperative patients in this population.[22] The patients are thus likely to reduce their milk consumption both spontaneously and due to the doctors' advice.[22] Because milk is the main dietary source of calcium,[24] a partial gastrectomy might thereby entail a relative deficiency in calcium intake. Recent evidence from epidemiologic and other data indicates that dietary calcium has a protective role in large bowel carcinogenesis, probably by affecting late stages in the malignant transformation.[24,25] Calcium deficiency is thus one conceivable result of this change in eating habits that might explain the increasing risk over time of developing colorectal cancer.

A variety of biochemical changes occur in the stomach following partial gastrectomy. The intragastric pH increases, which promotes the growth of bacteria that both reduce dietary nitrate to nitrite and convert dietary amines into the powerful carcinogens, the N-nitroso compounds.[26] Furthermore bile reflux in combination with the changing bacterial flora may lead to formation of N-nitroso bile acid conjugates also known as potent carcinogens.[27]

Finally changes in gastrin levels may explain the change in risk over time. Gastrin may have a promoting effect on colon cancer.[28] Patients with pernicious anemia have hypergastrinemia and seem to have an increased risk for colorectal cancer.[11] After partial gastrectomy, the basal serum gastrin concentration is slightly decreased following the Billroth I procedure, whereas a Billroth II procedure entails a more marked reduction.[29] The reduction in risk of colorectal cancer after the Billroth II procedure in this study (Table 3) is consistent with this reduction in gastrin levels. Over time serum gastrin concentration may rise gradually, mainly due to an increasing amount of gastrin released from duodenal g cells.[30] If gastrin does affect the risk of colorectal cancer, this finding is also consistent with the gradually increasing risk of colorectal cancer seen in this study.

Future studies of the association between gastrectomy and colorectal cancer should account for potential confounding factors such as SES and changes in eating habits. Osteoporosis may be a consequence of calcium deficiency, although data on this issue are still inconsistent (see, for example, Cummings et al.[31] and Raisz[32]). An analysis of osteoporotic fractures, now in progress, therefore may provide further clues about the impact of dietary changes after partial gastrectomy.

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The Role of Inhalation Injury in Burn Trauma

A Canadian Experience

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From 1977 to 1987, 1705 thermally injured patients were admitted to the Firefighters' Burn Center at the University of Alberta Hospitals. Thirteen hundred forty-four were male (78.8%) and 361 were female (21.2%), with a mean total burn surface area (TBSA) of 15.1 (SEM ± 0.4%) and a range of 1% to 99% TBSA. Sixteen hundred thirty-five patients survived to be discharged from hospital, with an overall survival rate of 95.9%. One hundred twenty-four burn patients (7.3%) suffered concomitant inhalation injury diagnosed by bronchoscopy. Patients with inhalation injury suffered from larger TBSA (39.7% ± 2.8% *versus* 12.2% ± 0.3%; $p < 0.01$) than those without inhalation injury. Inhalation injury increased the number of deaths from burn injury (34.7% *versus* 1.7%; $p < 0.01$) independent of age and TBSA. Inhalation injury was associated with a threefold prolongation of hospital stay (23.7 ± 0.7 *versus* 74.4 ± 6.2 days; $p < 0.01$) and was independent of age and TBSA. Multifactorial probit analysis was performed for both inhalation- and noninhalation-injured burned patients to allow TBSA and age adjusted rates of mortality for the burn population presented. The maximum detrimental effects of inhalation injury in burn patient outcome occurred when it coexisted with moderate (15% to 29% TBSA) to large (30% to 69% TBSA) thermal injuries. These data demonstrate that inhalation injury is an important comorbid factor in burn injury that increases the number of deaths substantially. Most importantly such injuries also independently prolong the duration of hospitalization in a highly unpredictable fashion as compared to patients with cutaneous burns only. As such our data illustrate the extreme importance of inhalation injury as a comorbid factor following thermal injury and reveal the present limitations for accurate quantification of the magnitude of respiratory tract injury accompanying thermal trauma.

DURING THE LAST decade, improvements in resuscitation of burn-injured and other trauma patients has led to increased incidence of survival from burn shock after major thermal injury; however sepsis and pulmonary failure remain important and principal causes of mortality and morbidity following thermal injury.[1]

Thermally damaged skin as well as inhaled products of combustion are known to activate neutrophils, in part through the alternate pathway of the complement system, subsequently damaging pulmonary tissues through release of proteases and free oxygen radicals.[1-3] Similarly stimulation of pulmonary macrophages following respiratory tract injury produces prostanoids and cytokines that further contribute to the pathophysiology of inhalation injury and the morbidity and mortality of the host by mechanisms incompletely understood.[4] Although this increase in burn mortality rate has been quantitated up to 60% beyond that expected in patients with cutaneous burns only,[5] the impact of inhalation injury on morbidity, length of hospitalization, and cost of care has not been thoroughly addressed.

The following study therefore was undertaken to investigate further the role of inhalation injury on both mortality and morbidity following thermal injury and to establish the overall duration of hospitalization and rate of recovery following thermal injury in a burn center functioning within the Canadian health care system.

Materials and Methods

The records of 1713 patients were reviewed during the 11-year period from January 1, 1977 to December 31, 1987. Epidemiologic, demographic, and therapeutic patient data were recorded in a computerized burn registry.

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This registry was on a personal computer that was linked, *via* network, to an Amdahl 5870 mainframe computer (Sunnyvale, CA) operating under the Michigan Terminal System (MTS) (University of Michigan, Ann Arbor, MI). Of the 1713 records reviewed, eight patients with extreme injuries who received compassionate care only were excluded. Patients cared for were referred to the burn center from the central and northern regions of the province of Alberta and the North West Territories of Canada and were resuscitated uniformly using the Parkland formula.[6] Burn wounds were treated with topical application of silver sulfadiazine every 12 hours until excision and grafting of deep second- and third-degree wounds were commenced, usually within the first postburn week.

Inhalation injury was suspected in patients with a history of impaired level of consciousness, injury occurring in closed space or structural fires, and in those patients sustaining facial burns. The diagnosis of inhalation injury was confirmed by the presence of mucosal erythema, edema, or ulceration and submucosal hemorrhage found on bronchoscopy normally performed within the first 24 hours after burn.[7] The charts of all patients requiring ventilatory support within the first 7 days after injury also were reviewed for the possibility of inhalation injury.[8] Although arterial blood gases and carboxyhemoglobin were measured and chest x-rays performed, they were unreliable for the establishment of the presence of inhalation injury. Pulmonary function studies and ^{133}Xenon lung scans were used only in a small number of patients and were not regularly performed for practical reasons.

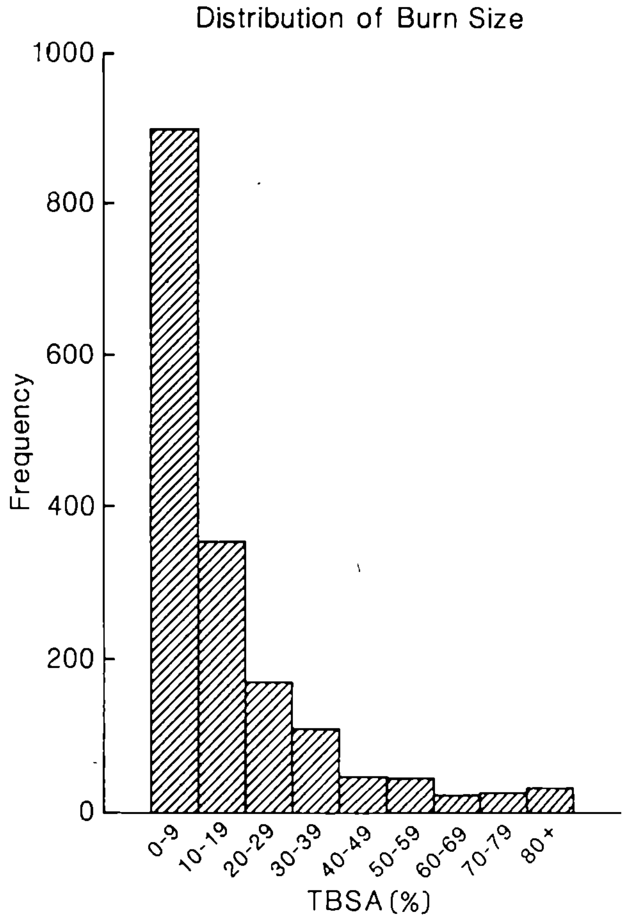


FIG. 2. Distribution of burn sizes (TBSA %). Overall TBSA for 1705 patients was 15.1% ± 0.4%.

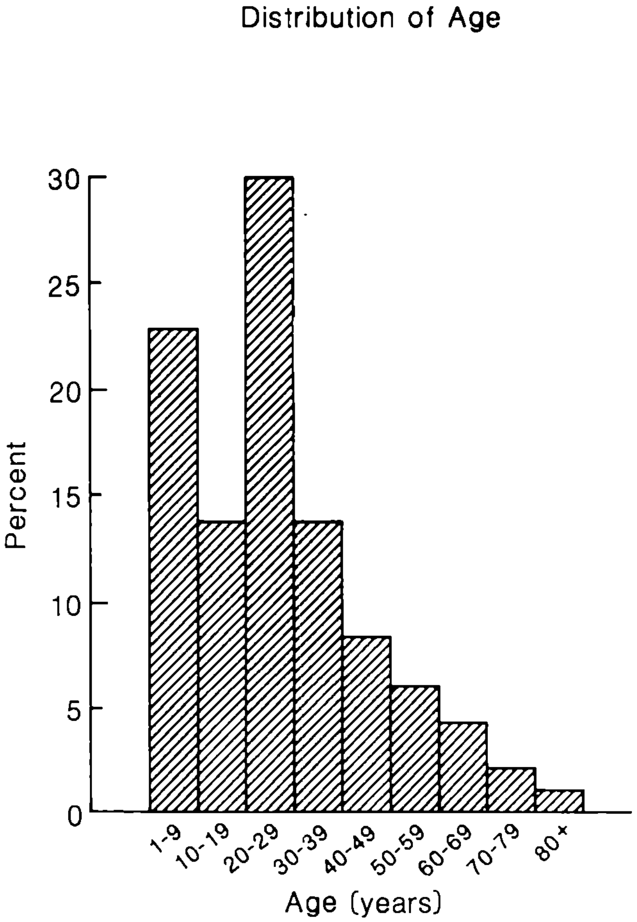


FIG. 1. Distribution of ages for 1705 patients included in the study. Mean age, 26.2 ± 0.5 years.

Statistical analysis was performed using the MANOVA, CROSSTABS, UANOVA, and PROBIT procedures in SPSS-X® (SPSS Statistical Program, Chicago, IL) and the logistical regression procedure in BMDP® (BMDP Statistical Software, Inc., Los Angeles, CA). The relative effects of burn size, age, and inhalation injury on death were analyzed with multifactorial probit analysis.[9,10]

Results

Of the 1705 patients in the study, 1344 were male (78.8%) and 361 were female (21.2%), of which 1635 patients survived, giving an overall survival rate of 95.9%. The frequency distribution of age, as shown in Figure 1,

TABLE 1. *Comparison of Descriptive Statistics from Four Burn Centers*

Statistic	UAH	MGH[11]	Brooke[5]	Salt Lake City[12]
Number	1705	619	1058	1458
Mean age (years)	26.2	39.0	31.0	24.4
Mean TBSA (%)	15.1	17.0	23.7	19.0
Mean LOS (days)	26.2	23.0	N/A	14.7
% Inhalation	7.3	N/A	24.6	7.0
Mortality rate (%)	4.1	7.0	22.6	8.0

demonstrates that the largest group of patients within our population was between the age of 20 and 29 years (30%), 86% of whom were male. Of the 1705 patients, 36% were in the pediatric or adolescent age range of 0 to 19 years, 51% adults were in the working years of life and only 7% of the patients were 60 years or older. The mean age of the population studied is 26.2 ± 0.5 years (range, 0 to 90 years). Most burn injuries in our study occurred at home (48%), with 34% occurring at work and 19% at other locations apart from the home or work place. Sixty per cent of these injuries were thermal burns, 19% were due to scalds, 7% to electrical injuries, and 14% were due to other injuries (including tar, grease, steam, friction, and other chemicals).

The mean size of burn injury was 15.1% ± 0.4% (range, 1% to 100%), with 26.2% of the injuries in the range from 20% to 100% of the total body surface and only 3.2% of the injuries were massive (70% or more) (Fig. 2). The mean age of the patient population and burn size does not differ significantly in each of the years of the study.

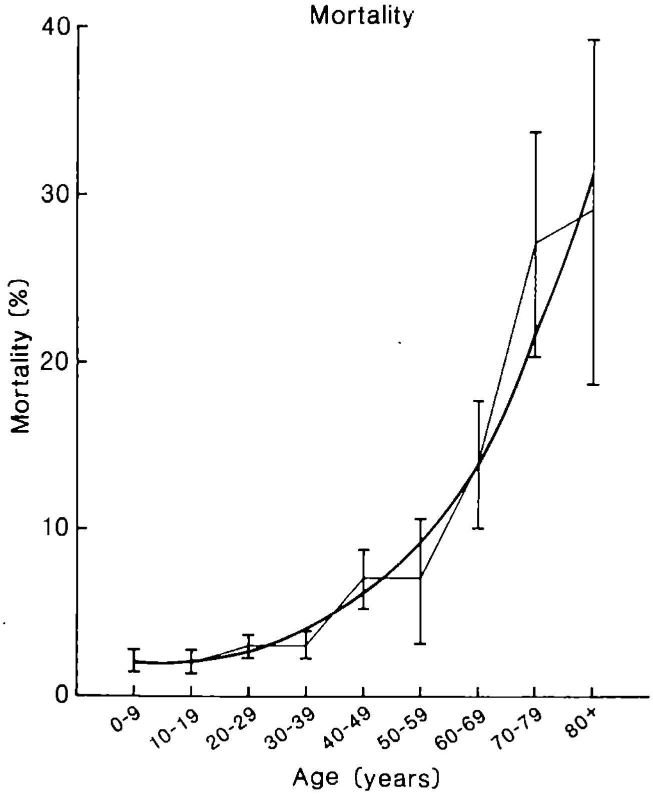


FIG. 3. Mortality in burn patients *versus* age. The overall mortality rate was 4.1%.

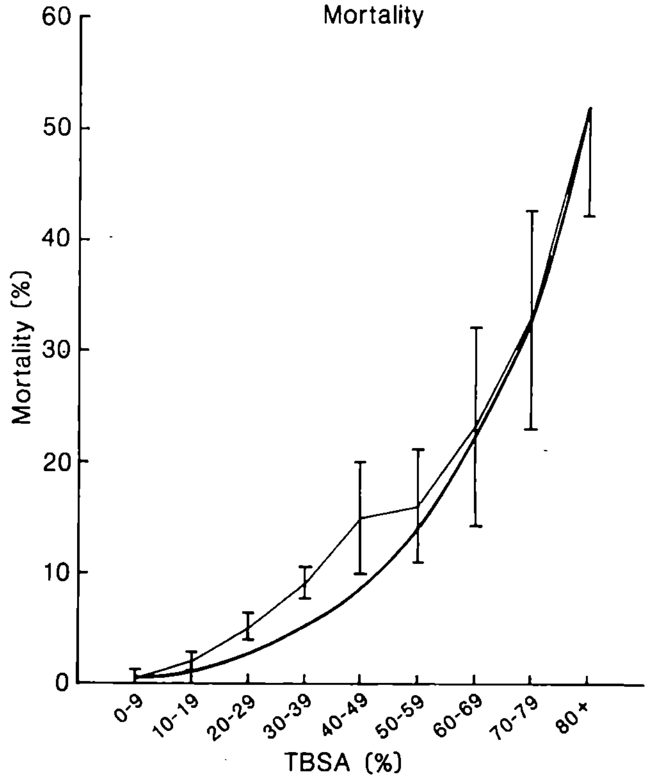


FIG. 4. Mortality in burn patients *versus* TBSA. The overall mortality rate was 4.1%.

The overall mortality rate in this study is 4.1%, which compares favorably with other large studies (Table 1).[5,8,11,12] Figures 3 and 4 illustrate that the number of burn deaths increases exponentially with increasing age of the patient and size of the burn injury.

One hundred twenty-four individuals of the 1705 patients studied suffered concomitant inhalation injury based on the criteria established earlier.[8] The mean age of the patients who suffered both inhalation injury and thermal burns was 30.1 ± 1.4 years, somewhat higher than for the patients with only cutaneous burns (25.2 ± 0.5 years; $p > 0.05$, not significant [NS]) (Fig. 5). However, for each grouping of TBSA, that is small (1% to 14%), moderate (15% to 29%), large (30% to 69%), and massive (70%), no statistically significant difference in age of the patients existed between those patients with inhalation and burns and those with burns only, thus allowing further comparison of the mortality of burns with and without inhalation injury, without the confounding effects of age.

In each age grouping of burned patients, the size of burn was substantially larger for patients with inhalational injury. The overall burn size was 39.7% ± 2.8% for patients

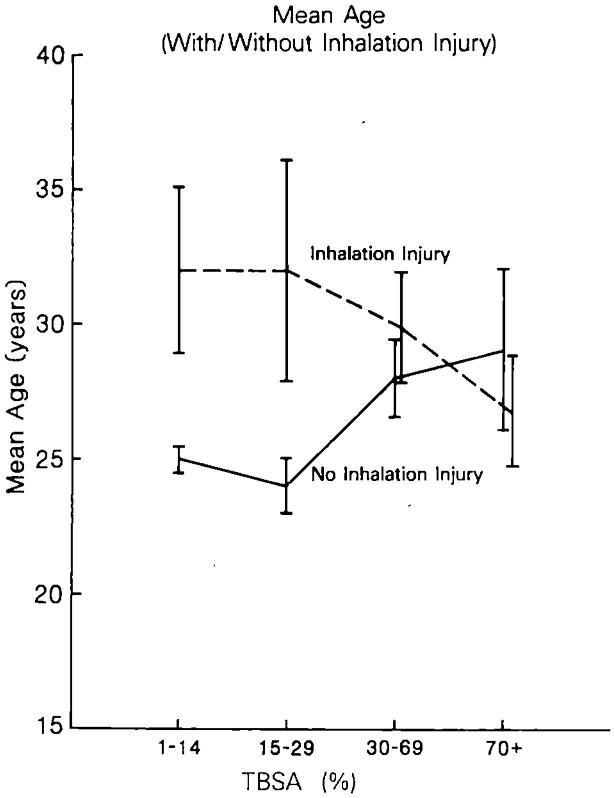


FIG. 5. Mean age *versus* %TBSA for patients with and without inhalation injury. The oveall age of the patients without an associated inhalation injury was 25.2 ± 0.5 years compared to 30.1 ± 1.4 years for those patients with an inhalation injury.

with inhalation injury compared to 12.2% ± 0.3% for those who had burn injury only ($p < 0.01$) (Fig. 6).

By analysis of variance, a substantial and significant difference in mortality rate was evident for patients in various age groupings (Fig. 7) and for each size of burn (Fig. 8) (1.7% mortality rate with no inhalation injury compared to 34.7% mortality rate with inhalation injury; $p < 0.01$).

Step-wise logistic regression of burn patient survival with and without respiratory tract involvement for each size of burn, *i.e.*, small, moderate, large, and massive, demonstrates that inhalation injury significantly influenced survival in all patients except those with small burns (Fig. 9). Qualitatively the influence of inhalation injury on the probability of survival given age and burn size is best seen in the three-dimensional plots of survival with burn injury (Fig. 10). As illustrated a sizeable plateau exists in which the small size of burn and the young age of the patient is associated with a high probability of a successful outcome until both extremes of burn size and age produce a sharp decline to valley of low survival. For inhalation injury the region of high survival is smaller, the decline in mortality occurs earlier for advancing age and TBSA, and the region of minimal probability of survival is larger, as contrasted with patients with no respiratory injury (Fig. 10). From the step-wise logistic regression, these data can be represented by the predictive equation:

$$p = \frac{e^u}{1 + e^u}$$

where:

$$u = 6.00 - 6.90 \times 10^{-2}\,(\text{TBSA}) - 8.08 \times 10^{-8}\,(\text{A})^3,$$

for the whole population and

$$u = 4.99 - 4.26 \times 10^{-2}\,(\text{TBSA}) - 1.30\,(\text{I}) - 8.65 \times 10^{-6}\,(\text{A})^3 - 2.12 \times 10^{-4}\,(\text{TBSA})\,(\text{A}),$$

for those patients with and without inhalation injury, where p is the probability of survival, I = 1 with inhalation injury and 1 if no inhalation injury is present, TBSA is total body surface area burned, and A is the age of the patient.

Finally morbidity of burn injury, in part depicted by length of stay (LOS) in hospital, is shown for all patients in Figure 11 and illustrates a gradual decline in the last 7 years of the study period. However, when one examines

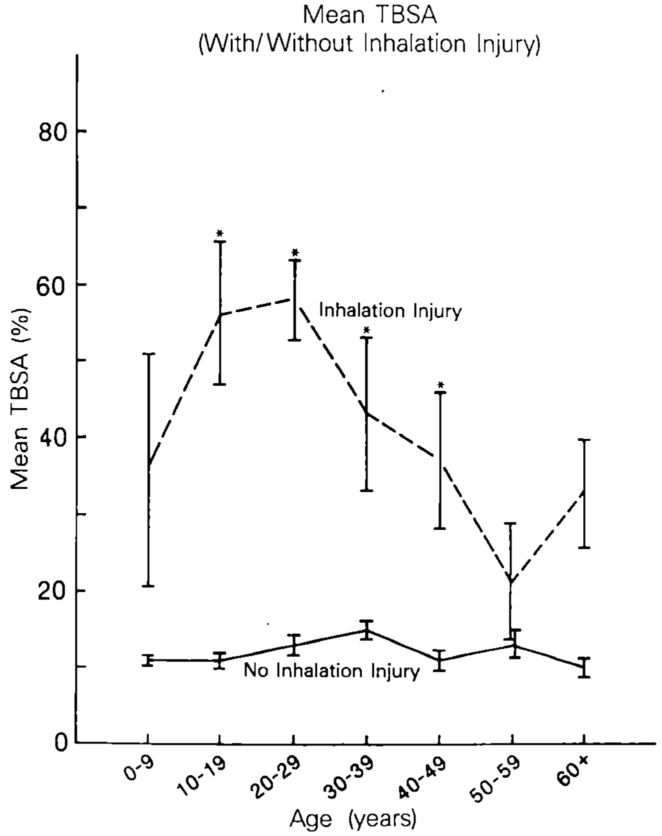


FIG. 6. Mean %TBSA *versus* age for burn patients with and without inhalation injury. The overall TBSA for those patients without an associated inhalation injury was 12.2% ± 0.3% compared to 39.7% ± 2.8% for those patients with an inhalation injury.

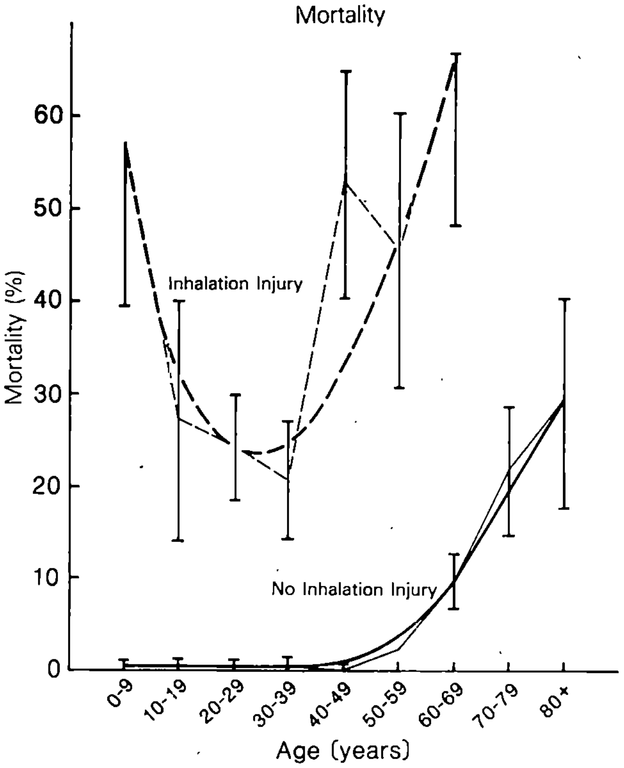


FIG. 7. Mortality *versus* age for burn patients with and without inhalation injury. The overall mortality rate for those patients without an inhalation injury was 1.7% compared to 34.7% for those patients with an inhalation injury ($p < 0.01$).

the length of stay of all patients (26.2 ± 0.8 days) and the subgroups of patients with and without inhalation injury, a significant difference exists in the duration of hospitalization (23.7 ± 0.7 *versus* 74.4 ± 6.2 days; $p < 0.01$) in those patients with concomitant lung injury. In addition the variability in LOS is much greater in each year of the study for those burned patients with respiratory involvement compared to those without. As was expected the LOS increased with increasing size of burn and inhalation injuries increased LOS for all size of burn, including the massive injury (Fig. 12). Similarly LOS increased dramatically for patients with inhalation injury at all ages (Fig. 13), but especially for pediatric patients who otherwise survive burn injury extraordinarily well.[13]

Discussion

From the data presented, it is apparent that the demographics of Canadian thermally injured patients (Fig. 1) resemble those found in other regions and, for the most part, are composed of either young pediatric-aged patients or young adults, mainly men in the prime productive years of life. The patient population in western Canada is somewhat younger when compared to similar facilities, and, unlike other centers, the age of the patient and size of burn injury do not decrease[11,13] but instead remain stable during the 11-year period of the study.

Table 1 illustrates our results as compared to other recently published series,[5,8,11] and although such comparisons between burns centers are useful, they also demonstrate the limitations that exist when comparing overall results in populations of burn patients that may be older, have larger burns, or differing rates of inhalation injury, a factor we now recognize to be of sizeable importance in assessing burn deaths.[9,14,15] Within these limits Canadian burn care, as based on our data, has comparable mortality rates and duration of hospitalization, although somewhat longer, possibly due, in part, to the system of health care in Canada.[16] However strict comparison of mortality rates requires adjustment for age, size of burn, and rates of inhalation injury for adequate assessment. Such statistical analysis requires multivariant probit analysis, as used here,[9,10] or multifactorial regression analysis used by others with similar results.[11-13] These forms of analysis both postulate an S-shaped relationship between independent variables and mortality but differ only slightly in the equations used.[11,17]

Although burn mortality in our study increased markedly with advancing age and burn size, in pediatric cases between the ages of 0 and 9 years, inhalation appears to

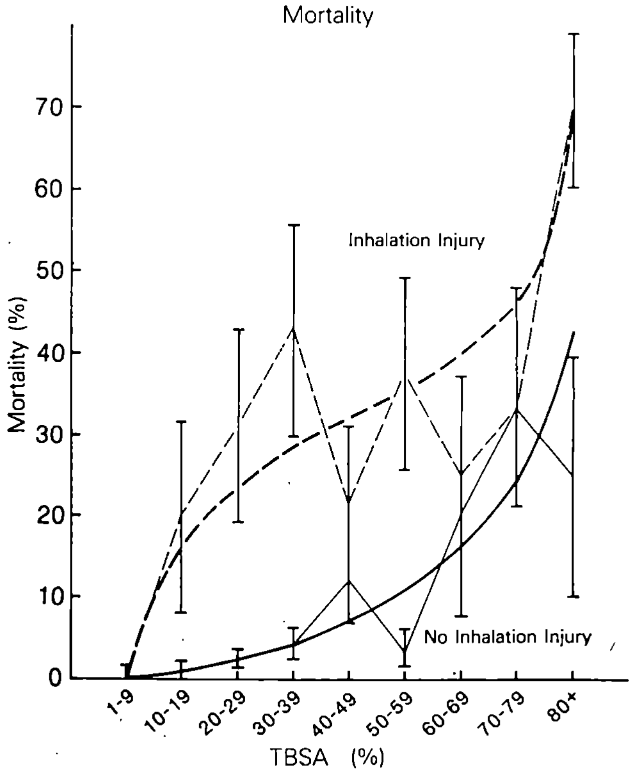


FIG. 8. Mortality *versus* %TBSA for burn patients with and without inhalation injury. The overall mortality rate for those patients without an associated inhalation injury was 1.7% compared to 34.7% for those patients with an inhalation injury ($p < 0.01$).

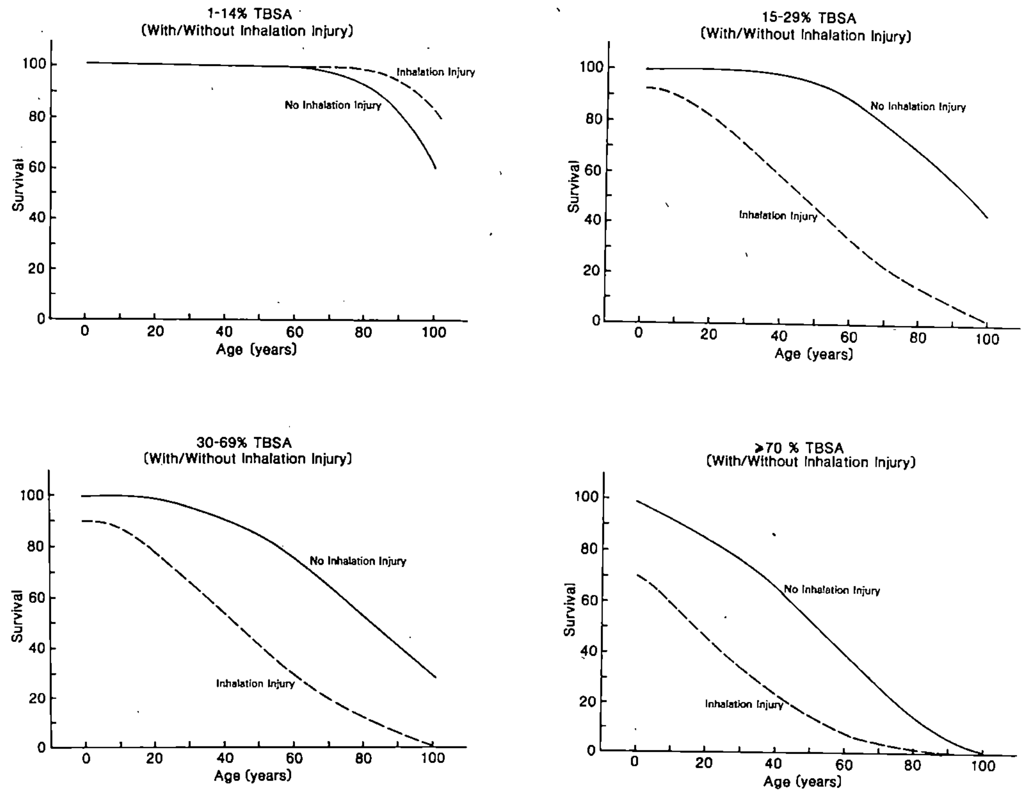
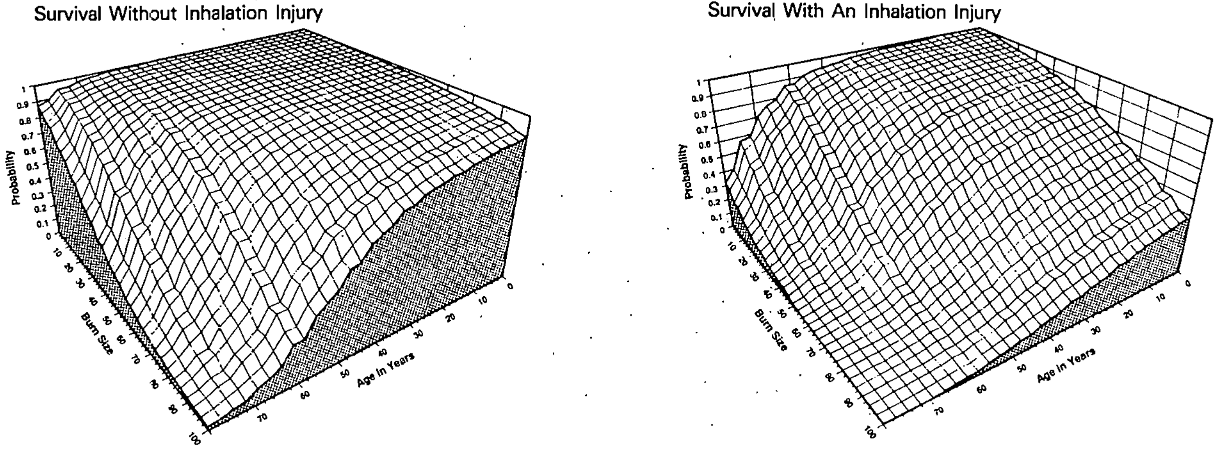


FIG. 9. Mortality *versus* age for each of four categories of %TBSA, (small, 1% to 14%; moderate, 15% to 29%; large, 30% to 69%; and massive, ≥ 70%) in burn patients with and without inhalation injury.

reverse the otherwise favorable survival rates (Fig. 7) and prolongs the length of stay in hospital (Fig. 13). Both these factors are probably due to the inherent difficulties in young children of maintaining good tracheobronchial toilet to ensure adequate ventilation through smaller airways and narrower endotracheal tubes.

We have demonstrated, as have others,[5,8,10,12,18] that inhalation injury contributes to mortality in burns, but its influence is predominantly on patients with moderate and large burns who otherwise have favorable prognosis without inhalation injury (Fig. 9). This is best demonstrated by shift in the slope of declining survival with inhalation injury in this range of burn size independent of age, as demonstrated in the three-dimensional probit analyses as compared to those patients with burn injury only. Furthermore, although most attention has been directed to mortality caused by inhalation injury in burn patients, the morbidity of inhalation injury and its effect on length of stay in hospital has not been realized totally. Through analysis of covariance, our data suggests that



FIGS. 10 A and B. Three dimensional plot of probability of survival following burn injury in patients without associated inhalation injury (A) and with inhalation injury (B).

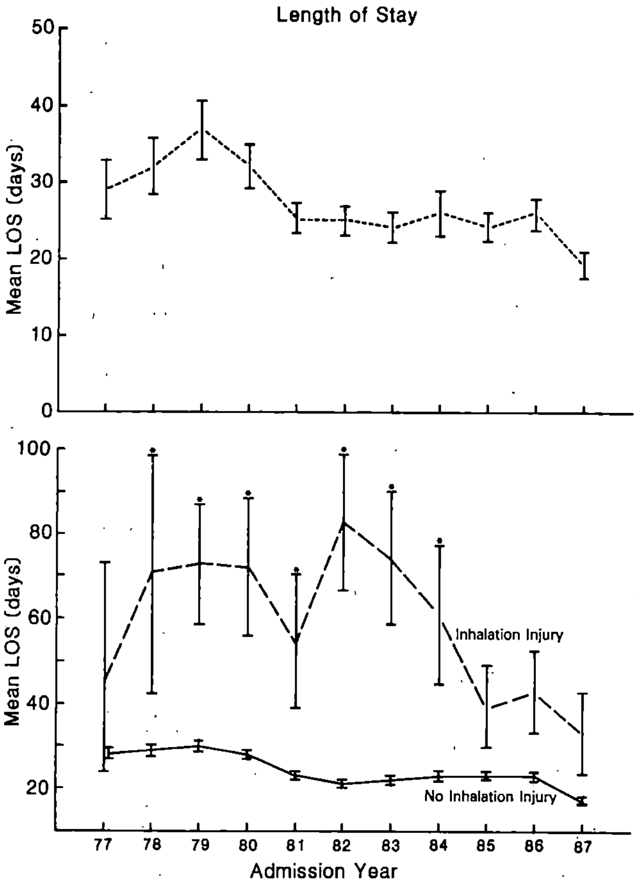


FIG. 11. Length of stay in days *versus* year of admission. Top graph includes all admissions and the bottom graph shows the same population divided into those burn patients with and without inhalation injury. Data shown are the mean and the SEM for each year. The mean length of stay for the total number of patients was 26.2 ± 0.8 days. The mean length of stay for those patients without an associated inhalation injury was 23.7 ± 0.7 days compared to 74.4 ± 6.2 days for those patients with an inhalation injury ($p < 0.01$).

duration of stay in hospital is increased threefold on average for those surviving patients with inhalation injury and this prolongation of the morbid period is independent of the age (Fig. 13) and the size of the burn injury (Fig. 12). More importantly the duration of hospitalization in our center can be predicted within a very narrow range if patients have no respiratory tract involvement with their cutaneous burns, but when inhalation injury coexists, the mean length of stay is substantially longer and highly variable, as expressed by the wide standard error of the mean for each measurement (Figure 11). These factors become important in overall assessment of cost of care and make resource and manpower planning difficult.[19] They also illustrate the difficulty in assessing the severity of the respiratory tract 'burn' and the limitations of bronchoscopic assessment only in inhalation injury.[20] Although Shirani et al.[5] used ^{133}Xenon lung scanning to detect respiratory tract damage in the absence of abnormalities at bronchoscopy, such cases represented a less severe form of injury than detectable by bronchoscopy. In the presence of bronchoscopic pathology,—this investigation added little to the diagnosis and, in their assessment, did not warrant the practical difficulties encountered in obtaining the results.[5]

In laboratory models of inhalation injury, Zawacki et al.[21] and others[22,23] found that severity of inhalation injury was a function of both the size of burn and the amount of smoke inhaled, and within limits carboxyhemoglobin levels were proportional to severity of injury. However the usefulness of carboxyhemoglobin levels as a predictor of the severity of inhalation injury has not been substantiated in burn patients,[18] in keeping with our own experience. Thus few clinical indices exist as yet that allow quantitative analysis of the magnitude of pulmonary injury after smoke inhalation. Early identification and quantification of the magnitude of injury in our inhalation-injured patients would allow identification of those patients who develop increased deadspace ventilation, prolonged requirements for mechanical ventilation, and are at risk of developing chronic pulmonary insufficiency, physiologic abnormalities that were documented in a subsegment of our inhalation-injured burn patients.[24] As

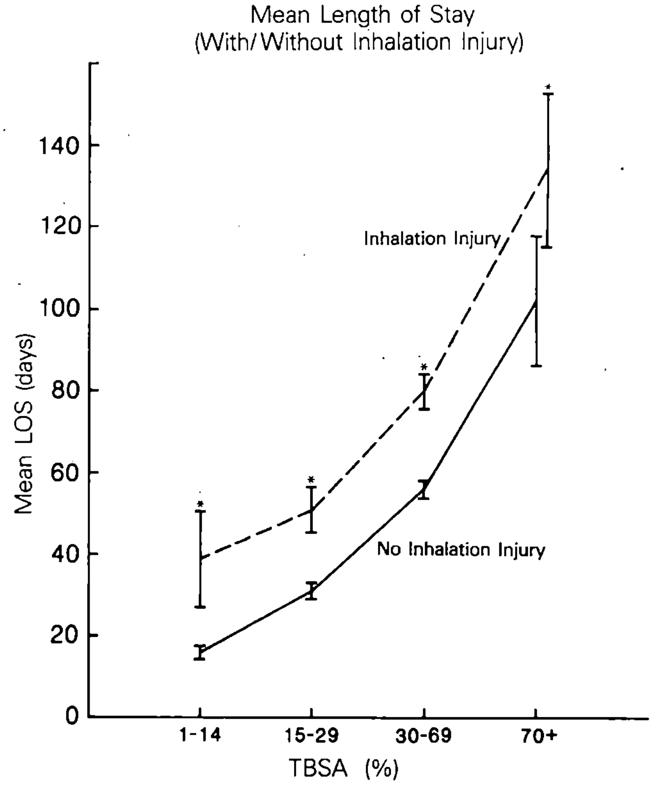


FIG. 12. Mean length of stay (LOS) *versus* %TBSA for small, moderate, large, and massive burns. Data shown are the mean for each group and the SEM. The mean LOS for those patients without an associated inhalation injury was 23.7 ± 0.7 days compared to 74.4 ± 6.2 days for those patients with an inhalation injury ($p < 0.01$).

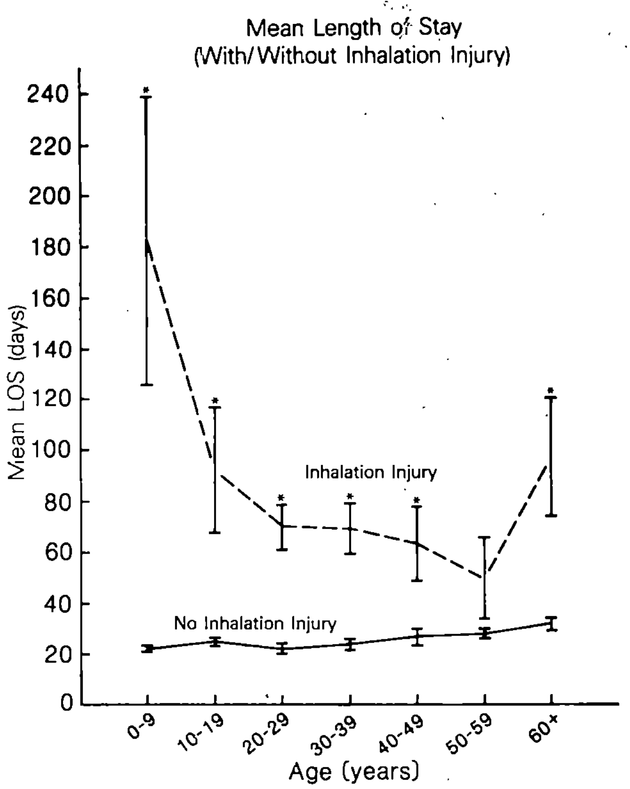


FIG. 13. Mean length of stay (LOS) *versus* age for burn patients with and without inhalation injury. Data shown are the mean for each age grouping and the SEM. The mean LOS for those patients without an associated inhalation injury was 23.7 ± 0.7 days compared to 74.4 ± 6.2 days for those patients without an inhalation injury ($p < 0.01$).

the understanding of the pathophysiology of this injury increases, analysis of free radicals, prostanoids, or cytotoxic lymphokines in the pulmonary tissues[1-3,25] and the interaction of the burn wound with pulmonary function[26] will allow increased understanding of both the severity of inhalation injury in burn patients and its treatment.

Our data further documents that inhalation injury increases burn mortality independent of patient age and burn size. In surviving thermally injured adults and children, hospitalization is prolonged substantially by inhalation injury, again independent of the age and TBSA in a highly variable and as yet unpredictable fashion.

Acknowledgments

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Involvement of Thromboxane and Neutrophils in Multiple-system Organ Edema with Interleukin-2

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Interleukin-2 (IL-2) produces toxicity characterized by generalized edema within 24 hours. This study tests whether the rate of IL-2 administration modulates the onset of edema and examines thromboxane (Tx) and neutrophils as possible mediators of this event. Recombinant human IL-2, 10^5 U ($n = 7$), 10^6 U ($n = 9$), or vehicle ($n = 8$) were given to anesthetized rats intravenously during a period of 1 hour. At 6 hours edema, as measured by increase in wet to dry weight (w/d) ratio, was present in the heart, liver, and kidney, with 10^5 U IL-2 and in the lung, heart, liver and kidney with 10^6 U IL-2, relative to values with vehicle-infused controls (all $p < 0.05$). With a 1-hour infusion of 10^6 U IL-2, there was an increase in plasma thromboxane (Tx)B_2 level to 1290 ± 245 pg/mL, higher than 481 ± 93 pg/mL in control rats ($p < 0.05$); lung polymorphonuclear leukocyte (PMN) sequestration of 53 ± 7 PMN/10 high-power fields (HPF) relative to 23 ± 2 PMN/10 HPF in controls ($p < 0.05$); and increased bronchoalveolar lavage (BAL) fluid protein concentration of 1970 ± 210 µg/mL relative to 460 µg/mL in controls ($p < 0.05$). When 10^6 U IL-2 was given as a 1-minute intravenous bolus ($n = 9$), edema was not demonstrated, plasma TxB_2 levels were similar to controls, there was no leukosequestration, and BAL protein levels were normal. These data indicate that a constant infusion but not the rapid bolus administration of IL-2 produces in rats multiple-system organ edema, increased plasma TxB_2, sequestration of PMNs, and microvascular permeability. These findings may explain the early toxicity seen in patients given high-dose IL-2 in cancer treatment.

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INTERLEUKIN (IL)-2 IS A potent cytokine with diverse inflammatory effects, including early polymorphonuclear leukocyte (PMN) activation and later generation of lymphokine-activated killer (LAK) cells, a cell type able to promote tumor regression.[1,2] The latter cell type has led to IL-2 use in cancer immunotherapy.[3,4] Because the growth of activated lymphocytes *in vivo* depends on constant exposure to IL-2 and the serum half-life is short (6 to 10 minutes), repeated injections are required.[5,6] However the doses of IL-2 necessary for effective cancer treatment have produced severe toxicity characterized by generalized permeability increase with pulmonary edema, pleural effusions, ascites, and weight gain.[4]

When IL-2 is administered by bolus injection, toxicity becomes manifest in mice after 3 or 4 days. The rapidity of appearance and severity of toxic reactions are related to the frequency of injection and to the total IL-2 dose given.[6,7] Thus patient toxicity is greater when IL-2 is administered intravenously continuously and is greater in rats when IL-2 is administered intravenously twice daily in dosages of 3 × 10^6 U/kg rather than once daily 150 × 10^6 U/kg.[6,8] Cellular elements implicated in the toxic reaction have been lymphocytes. When activated by IL-2, they proliferate and are able to lyse tumor cells after several days. The proliferation of activated lymphocytes is temporally associated with the development of late side effects. Furthermore selective depletion of one subset of IL-2–activated lymphocytes, those bearing the asialo GM1 surface glycolipid, prevents the toxicity seen after 5 days of IL-2, with reduction in pulmonary edema and ascites.[9]

Recent studies using the sheep lung lymph fistula indicate that pulmonary microvascular permeability increases within 2 to 3 hours after an IL-2 infusion, an event associated with increased plasma thromboxane (Tx)B_2. This is earlier than previously reported, suggesting that mechanisms independent of LAK cells are involved in early toxicity.[1,10,11] Credence is given to this possibility by evidence from clinical studies that patients given IL-2 de-

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velop edema, evident by weight gain, within 24 hours of starting treatment, a time interval insufficient for LAK cell generation.[4] Such mechanisms might involve PMNs because these are known mediators of early inflammatory events following a variety of other stimuli. Because the presence of continuous high plasma levels of IL-2 seems to be required for effective lymphocyte activation, a better understanding of the mechanisms of early toxicity is needed. The purpose of this study, therefore, was to determine if IL-2 induces rapid edema and to examine the involvement of TxA_2 and PMNs in this early event.

Methods

Animal Preparation

Thirty-three adult male Sprague-Dawley rats (Charles River Laboratories, Wilmington, MA) that weighed approximately 500 g were anesthetized with intraperitoneal ketamine (35 mg/kg). A jugular venous catheter was inserted for fluid or drug infusion (1 mL/hr) and hourly intravenous anesthetic administration (ketamine, 8 mg/kg; xylazine 1 mg/kg). All animals were supine for the duration of the experiment.

Preparation of Solutions

Recombinant human IL-2 (Hoffman-LaRoche, Nutley, NJ) was reconstituted just before use with 1 mL normal saline per 10^6 U IL-2. The saline vehicle contained mannitol (5 mg/mL) and human albumin (25 mg/mL). In animals infused with 10^5 U IL-2, the stock solution of 10^6 U/mL was diluted 10 times so each rat received the same 1-mL volume. Endotoxin content was 3.3 pg/10^6 U IL-2 measured by the Limulus amebocyte lysate assay (Associates of Cape Cod, Falmouth, MA).

Prostanoid Assay

Concentration of TxB_2 and 6-keto-$PGF_{1\alpha}$ in plasma were measured in duplicate with a double radioimmunoassay kit, using an antibody whose cross-reactivity with heterologous prostanoids was less than 1% (Seragen, Cambridge, MA).[12]

Experimental Protocol

Four groups were studied. In the first three groups, IL-2 10^5 U ($n = 7$), 10^6 U ($n = 9$), or vehicle ($n = 8$) were infused by pump during 1 hour (model 352, Sage Instruments, Orion Research, Inc., Cambridge, MA). The fourth group was infused with 10^6 U IL-2 as a bolus for 1 minute ($n = 9$). In preliminary experiments it was found that giving the vehicle by bolus gave identical, low wet weight to dry weight lung ratios as those obtained by administering vehicle during the course of 1 hour.

Six hours after the beginning of the experiment, animals were killed with an overdose of anesthetic. A thoracotomy was performed and blood for eicosanoid assay was obtained by cardiac puncture and was introduced into tubes containing 0.07 mol/L (molar) ethylene diamene tetracetic acid and 0.09 mol/L aspirin. The left lung bronchus was clamped. Bronchoalveolar lavage (BAL) of the right lung was performed with 3 mL of saline. This was repeated three times. The combined lavage return of about 8 mL was centrifuged at 1500*g* for 20 minutes at 4 C (PR-2, International Equipment Co., Needham Heights, MA), frozen at −20 C, and subsequently used for assay of protein concentration. This was measured by the spectophotometric protein dye method.[13]

The wet to dry weight (w/d) ratios of the left upper lung lobe, heart, left lobe of the liver, left kidney, and spleen were calculated after weighing the freshly harvested organ, heating at 90 C in a gravity convection oven (Precision Scientific Group, Chicago, IL) for 72 hours and weighing the residuum.

The left lower lung lobe was used for histology. After the rats were killed, the lobe was perfused with 10% formaldehyde and then inflated with the same material to a pressure of 25 cm H_2O. Following fixation the inferior aspect of the lobe was stained with hematoxylin and eosin for light microscopic analysis. All microscopic sections were interpreted in a blind fashion by a pulmonary pathologist (LK). Lung sequestration was quantitated by counting alveolar septal wall PMNs. Only peripheral lung parenchyma was examined. Microscopic fields containing other structures such as airways, large vessels, and pleura were excluded. Leukocyte entrapment was expressed as the mean number of PMNs per 10 high-power fields (HPF)(x 1000).

Results are expressed as mean ± SE in text and figures. Statistics were conducted by an analysis of variance and if this was positive, by a nonpaired Student's t test. Significance was accepted if $p < 0.05$.

Animals in this study were maintained in accordance with the guidelines of the Committee on Animals of the Harvard Medical School and those prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (Department of Health, Education and Welfare, Publication No. 78-23 [National Institute of Health]), 1978 revised edition.

Results

Interleukin-2 10^5 U infused during the course of 1 hour resulted in edema at 6 hours, in the heart (w/d ratio 4.20 0.19 relative to 3.76 ± 0.08 in vehicle infused controls), liver (3.44 ± 0.07 *versus* 3.18 ± 0.10), and kidney (4.31 ± 0.06 *versus* 4.00 ± 0.07) (all $p < 0.05$), but not lung

(Fig. 1). When 10^6 U IL-2 was given during 1 hour, there was edema in the lung (w/d ratio 4.93 ± 0.20 *versus* 4.06 ± 0.10), heart (4.09 ± 0.11), liver (3.50 ± 0.10) and kidney (4.25 ± 0.07) (all $p < 0.05$). The spleen did not develop edema (w/d ratio 4.12 ± 0.08 *versus* 3.95 ± 0.06, $p > 0.05$). Interleukin-2 10^6 U administered during 1 hour resulted in an increase in plasma TxB_2 level relative to controls ($p < 0.05$, Table 1); lung neutrophil sequestration of 53 ± 7 PMN/10 HPF, more than 22 ± 3 PMN/10 HPF in controls ($p < 0.05$, Fig. 2), and BAL fluid protein accumulation of 1970 ± 210 μg/mL, more than 460 ± 190 μg/mL in controls ($p < 0.05$, Fig. 3). Levels of 6-keto-$PGF_{1\alpha}$ were unaffected by IL-2 (Table 1). In contrast to the 1-hour infusion, when 10^6 U IL-2 was given by bolus injection, no edema was demonstrated in any organ: lung w/d ratio 3.78 ± 0.12, heart 3.64 ± 0.07, liver 3.14 ± 0.06 (all $p < 0.05$), and kidney 4.14 ± 0.15 (not significant [NS]). There was minimal increase in plasma TxB_2 ($p < 0.05$, Table 1) and BAL fluid protein accumulation was reduced to 820 ± 260 μg/mL ($p < 0.05$).

TABLE 1. *Effect of Rate of Administration of IL-2 on Plasma Prostanoid Concentration‡ After 6 Hours*

	TxB_2	6-keto-$PgF_{1\alpha}$
Vehicle	481 ± 93	63 ± 19
10^6U 1-hour infusion	1290 ± 245*	121 ± 37
10^6U bolus	615 ± 45†	164 ± 56

* and † indicate $p < 0.05$ relative to vehicle infused rats and 10^6U IL-2 given by 1-hour infusion.

‡ Units in pg/mL.

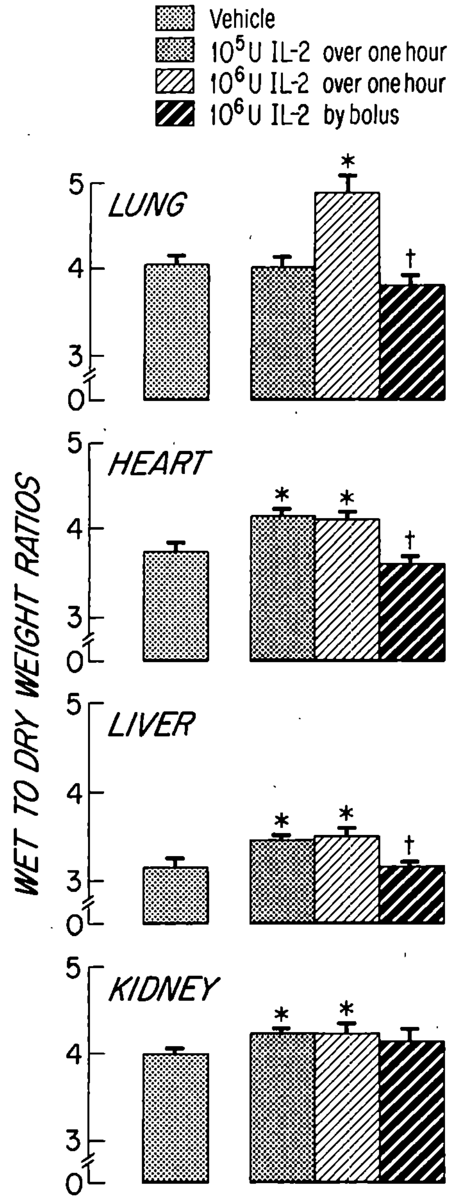

FIG. 1. Infusion of 10^5U IL-2 during 1 hour produced edema in heart, liver, and kidney, whereas infusion of 10^6U during 1 hour led to edema in the lung as well. In contrast 10^6U given by bolus did not produce edema in any organ. * and † refer to significance of $p < 0.05$ relative to vehicle-infused controls, and between 10^6 U IL-2 given during 1 hour and by bolus, respectively.

Discussion

Immunotherapy with IL-2 when used alone requires continuous maintenance of effective plasma levels to promote lymphocyte activation and proliferation.[5] Toxic effects of IL-2 become manifest in this setting. The data of this study indicate that IL-2 is capable of producing in rats increase in plasma Tx levels and multiple-system organ edema. In the lungs there is sequestration of PMNs, alveolar protein leak, and edema. These pathologic

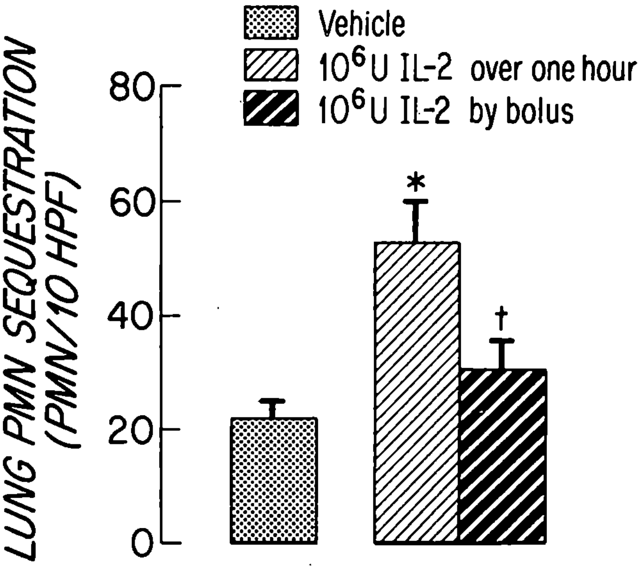

FIG. 2. 10^6U IL-2, when given by infusion but not when given by IV bolus, produced lung PMN sequestration. * and † indicate $p < 0.05$ relative to vehicle-infused control and 10^6 U IL-2 by infusion, respectively.

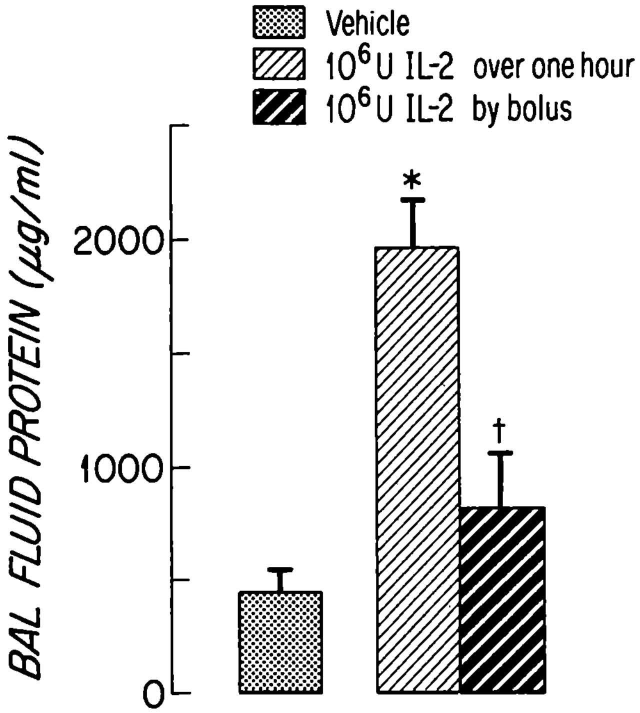

FIG. 3. 10^6U IL-2 produced protein leak in bronchoalveolar lavage fluid when given by infusion during 1 hour but not when given by bolus. * and † indicate $p < 0.05$ relative to vehicle-infused control and 10^6U IL-2 during 1 hour, respectively.

changes became evident 6 hours after a continuous IL-2 infusion during the course of 1 hour but not when IL-2 is given by bolus.

Interleukin-2 causes fatal pulmonary edema in mice after 5 to 7 days when 24 × 10^6 U/kg are administered twice daily by intraperitoneal injection.[9] Previous studies in our and in other laboratories have demonstrated increases in microvascular permeability within 2 to 3 hours after IL-2 is given by bolus push or infused for 30 minutes in the sheep. This is documented by increased protein-rich lymph flow from the lung. In these studies, however, the finding of transendothelial protein flux, an indicator of increased microvascular permeability, does not necessarily indicate edema formation, which is the net result of fluid efflux and influx. In the present experiments, we have demonstrated not only alveolar protein accumulation but also edema (Figs. 1 and 2).

Selectivity of organ edema was noted in the present study. Thus heart, liver, and kidney appeared to be more susceptible to IL-2 than the lung (Fig. 1). Current data do not permit an understanding of this mechanism of enhanced sensitivity.

Interleukin-2 toxicity is probably a consequence of sustained plasma IL-2 levels. Thus, while IV bolus injection leads to a rapid peak level, this is short lived because IL-2 disappears from the rat circulation within 1 hour after injection.[14] Similar results have been found with another cytokine, interleukin 1 (IL-1). Interleukin-1 (50 U) given as 10-U boluses during 2 hours produced lung edema. In contrast IL-1 (100 U) administered as a single IV bolus did not cause any alveolar protein leak or lung edema.[15,16] Thus *in vivo* activity of these cytokines appears to be related to sustained plasma concentrations.

In other studies subcutaneous or intraperitoneal administration of IL-2 led to much lower peak intravascular levels than an intravenous bolus, but the former routes were more effective in promoting lymphocyte activation *in vivo*, presumably due to the constant release of IL-2 into the circulation.[5] Lymphocyte activation and toxicity appear not to be necessarily linked.[9] Thus 3 × 10^3 U/kg/hr administered by constant infusion, a dose ineffective for lymphocyte activation and tumor lysis, was the maximum tolerated in patients in terms of toxic side effects compared to 10^6 U/kg given by bolus injection, which yielded few side effects.[6] In our study toxicity was not evident in any organ when 10^6 U was given by bolus, whereas one tenth of this dose given as an infusion for 1 hour produced multiple-organ edema (Fig. 1). Furthermore, in another IL-2 study in rats, 3 × 10^6 U/kg given twice daily intravenously produced more toxicity at 14 days than did 150 × 10^6 U/kg given once daily by the same route.[8]

The finding of pulmonary edema and alveolar protein leak in association with sequestration of PMNs in the pulmonary microvasculature strongly suggests a causal relationship (Figs. 2 and 3). PMNs are known to be central mediators of early permeability increase and edema after myocardial, hindlimb, and renal ischemia and following complement activation, trauma and sepsis.[17-21] However no report has implicated PMNs as mediators of IL-2 toxicity. That PMNs may play a role is supported by the *in vitro* evidence that isolated PMNs, when incubated with IL-2 for 4 hours, become activated to produce TxB_2.[1] Thus 10^3 U/mL IL-2 stimulate a fivefold increase in TxB_2 production in 10^6 PMN/mL. Based on calculations assuming a 6- to 10-minute plasma half-life,[4] it is likely that peak IL-2 levels in our 1-hour infusion study were 10^3 to 10^4 U/mL. Furthermore incubation of PMNs with the supernatant from IL-2 cultured lymphocytes increases PMN oxidative activity, an event mediated by another cytokine, tumor necrosis factor (TNF).[22] This cytokine will be secreted by cultured peripheral blood mononuclear cells when incubated with IL-2 at 10^3 U/mL.[23] Furthermore elevated TNF levels in plasma have been demonstrated within 2 hours of IL-2 administration in patients.[24] Also administration of anti-TNF antibody prolonged the survival of mice given repeated IL-2 injections.[25] Tumor necrosis factor can increase oxidative activity in PMNs within 10 minutes, an event lasting for at least 3 hours.[26,27]

Therefore we can believe that PMN activation occurred and that these cells were the source of Tx.

Activated PMNs may mediate microvascular protein leak directly, through release of oxygen radicals and lysosomal enzymes, or indirectly by synthesis of other vasoactive inflammatory mediators.[28,29] Thus TxA_2 synthesized by extravascular parenchyma or by PMNs is known to mediate lung leukosequestration and PMN activation in the setting of ischemia and reperfusion of the lower torso and following acid aspiration.[21,30,31] In the current study, lung leukosequestration and permeability increases were associated with high plasma Tx levels (Table 1, Figs. 2 and 3). In addition to indirect effects *via* PMNs, Tx may alter directly the microvascular barrier. *In vitro* studies show that Tx widens interendothelial junctions through modulation of cytoskeletal stress fibers.[32] Furthermore Tx is known to be responsible for the increased mean pulmonary artery pressure that follows IL-2 administration.[33] Thromboxane inhibition prevents the pulmonary hypertension and the increase in protein-rich lung lymph flow in sheep that is noted 30 minutes after IL-2 administration.[1]

Interleukin-2 itself has no demonstrable effect on microvascular permeability *in vitro*.[10] *In vivo* evidence indicates that IL-2 leads to the synthesis of other cytokins, for instance Γ-interferon[34] and TNF. This cytokine, but not IL-2, may lead, during 24 hours, to induction of the endothelial antigen, intercellular adhesion molecule-1 (ICAM-1).[35] This PMN adhesion receptor, essential for PMN adhesion to endothelium, may recruit PMNs and other inflammatory cells to sites of inflammation. Following PMN activation and adhesion, these cells might then cause edema. However Γ-interferon is an unlikely mediator of edema in the current study because edema was evident within 6 hours of IL-2 administration.

Evidence suggests that the cytokine IL-1 is also induced by IL-2 and thus may be operative *in vivo*.[36,37] Both IL-1 and TNF induce ICAM-1 and another receptor for neutrophils, endothelial leukocyte adhesion molecule-1 (ELAM-1), an activation antigen that has peak expression at 4 to 6 hours. Therefore it is plausible that several cytokines are involved. Skin biopsies in patients taken within 24 hours of starting IL-2 therapy displayed induction of both ICAM-1 and ELAM-1.[38]

The data of this study indicate that the infusion but not the rapid bolus administration of IL-2 promotes rapid multiple-system organ injury and alveolar permeability, events associated with increased plasma Tx concentration and lung neutrophil sequestration.

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Subject Index to Volume 212 (July–December 1990)

A

Abdomen
  abscess after blunt trauma, 60
  acute problems in paraplegia, 561
  computed tomography in comatose children (*Letters*), 118
  infections treated with imipenem/cilastatin, 581
Abscess
  hepatic, management of, 655
  intra-abdominal, after blunt trauma, 60
Acid aspiration, systemic organ injury from, tumor necrosis factor affecting, 513
Aging
  and duodenal bicarbonate secretion, 332
  and pancreatectomy in elderly patients, 140
  and responses to colon resection, 213
Ambulation, and recovery from postoperative ileus, 671
Amylase levels, normal, in acute pancreatitis (*Letters*), 648
Anesthetics affecting responses to liver ischemia, 23
Aneurysms, abdominal aortic, in coronary artery disease, 415
Angioplasty, laser thermal, 257
Animal studies
  anesthetics affecting responses to liver ischemia, 23
  bacterial translocation process, 496
  heart failure from pneumonectomy in shock, 197
  multisystem organ edema from interleukin-2, 728
  myocardial effects of protamine, 387
  oxygen affecting postoperative protein metabolism, 228
  platelet-activating factor in cholecystitis, 455
  prevention of postoperative complications in jaundice, 221
  tumor growth inhibition by intravenous prostaglandin E_1, 45
  tumor necrosis factor affecting acid aspiration-induced systemic organ injury, 513
  tumor necrosis factor in lung injury after intestinal ischemia–reperfusion, 694
  verapamil affecting vein bypass graft patency, 87
Anorectal carcinoid tumors (*Letters*), 650
Antibiotics
  in enterococcal infections, 155
  imipenem/cilastatin for intra-abdominal infections, 581
  parenteral cefoxitin in elective colorectal operations, 209
Aorta
  abdominal aneurysm in coronary artery disease, 415
  dissection of, vascular complications in, 705
APACHE II for evaluation of surgical patients, 266
Atherosclerosis
  coronary, reoperation for, 378
  lower-limb-threatening ischemia in, 402
  and partial ileal bypass for hypercholesterolemia, 318

B

Bacterial translocation to intestines, 496
Barrett's esophagus, surgery in, 528
Bicarbonate secretion, duodenal, aging affecting, 332
Biliary tract
  drainage in prevention of postoperative complications in jaundice, 221
  sclerosing cholangitis, 551
Blood pressure, intraoperative
  and postoperative complications, 567
  preoperative predictors of changes in, 66
Body composition, and responses to colon resection, 213
Book reviews, 114, 645
Breast conservation therapy for cancer
  in multiple tumors, 38
  and survival after locoregional recurrence, 166
Budd–Chiari syndrome, current management of, 144
Burns
  inhalation injury in, 720
  wound healing affected by growth hormone, 424
Bypass surgery
  cardiopulmonary, with deep hypothermic circulatory arrest, in retroperitoneal tumors, 472
  partial ileal, for hypercholesterolemia, 318
  vascular
    late failure of reversed vein grafts in (*Letters*), 122
    and verapamil affecting vein graft patency, 87

C

Calcitonin levels, and hypercalcitoninemia in medullary thyroid carcinoma, 395
Calcium levels, and mortality in critically ill patients, 543
Carcinoid tumors, anorectal (*Letters*), 650
Cardiopulmonary bypass with deep hypothermic circulatory arrest, in retroperitoneal tumors, 472
Carotid endarterectomy, restenosis after, 629
Cefoxitin, parenteral, with oral antibiotics in elective colorectal surgery, 209
Chloralose affecting responses to liver ischemia, 23
Cholangitis, sclerosing, 551
Cholecystectomy
  coelioscopic (*Letters*), 649
  secondary, morbidity with (*Letters*), 651
Cholecystitis, platelet-activating factor in, 455
Cholesterol levels, and partial ileal bypass for hypercholesterolemia, 318
Coelioscopic cholecystectomy (*Letters*), 649
Colectomy, total, and straight ileoanal pull-through in benign colorectal disease, 242
Colitis, ulcerative, ileoanal anastomosis in (*Letters*), 120
  pouch-related complications in, 446
Colon, primary repair of wounds in (*Letters*), 118
Colorectal cancer after partial gastrectomy, 714
Comatose children, abdominal CT in (*Letters*), 118
Computed tomography, abdominal, in comatose children (*Letters*), 118
Coronary artery disease
  and reoperations in atherosclerosis, 378
  and repair of abdominal aortic aneurysms, 415
Cystic conditions
  polycystic liver disease, highly symptomatic, 30
  tumors of pancreas, 432

D

Dendritic leukocytes in allograft rejection, 308
Diabetes, and preoperative predictors of intraoperative hypotension and hypertension, 66
Dialysis, and angioaccess in upper extremity ischemia, 187

- DNA, recombinant, significance in surgery, 178
- Drainage, biliary, in prevention of postoperative complications in jaundice, 221
- Dumping syndrome, postgastrectomy, octreotide in, 678
- Duodenal bicarbonate secretion in aging, 332

E

- Editorials, 1, 123, 559
- Eicosanoids, and cholecystitis produced by platelet-activating factor, 455
- Endarterectomy, carotid, restenosis after, 629
- Enterococcal infections, recommendations for therapy in, 155
- Esophagus
  - Barrett's, surgery in, 528
  - perforation of, pleural wrap in (*Letters*), 652
  - variceal bleeding
    - selective shunt versus nonshunt surgery in, 97
    - in urban hospital patients, 521
- Estrogen receptors in hepatocellular carcinomas, 150

F

- Fitz, Reginald, characterization of acute pancreatitis, 109
- FK 506 for immunosuppression in transplantations, 295

G

- Gallbladder
  - coelioscopic cholecystectomy (*Letters*), 649
  - platelet-activating factor in cholecystitis, 455
  - secondary cholecystectomy of, morbidity with (*Letters*), 651
- Gastrectomy
  - and octreotide in postoperative dumping syndrome, 678
  - partial, colorectal cancer after, 714
- Gastrinomas, immunocytochemistry of, 607
- Gastrointestinal tract
  - ambulation affecting recovery from postoperative ileus, 671
  - bacterial translocation in, 496
  - cefoxitin for colorectal operations, 209
  - colorectal cancer after partial gastrectomy, 714
  - duodenal bicarbonate secretion in aging, 332
  - intrarectal ultrasonography, 602
  - lung injury in intestinal ischemia–reperfusion, tumor necrosis factor in, 694
  - octreotide in dumping syndrome, 678
  - parietal cell vagotomy and dilatation for peptic duodenal stricture, 597
  - partial ileal bypass for hypercholesterolemia, 318
  - *pneumatosis intestinalis*, 160
  - postoperative small bowel obstruction (*Letters*), 121
  - primary repair of colon wounds (*Letters*), 118
  - responses to colon resection affected by age and body composition, 213
  - results of ileoanal anastomosis in polyposis and colitis (*Letters*), 120
    - and pouch-related complications, 446
  - splanchnic PGI_2 production after reperfusion in shock, 688
  - surgery in Barrett's esophagus, 528
  - total colectomy and ileoanal straight endorectal pull-through in benign colorectal disease, 242
  - tumor necrosis factor affecting intestinal structure and metabolism, 663
  - upper tract bleeding in urban hospital patients, 521
  - variceal bleeding treatment with selective shunt versus nonshunt surgery, 97
- General surgery, issues in (*Presidential Address*), 235
- Genetics, molecular
  - and cancer, 3
  - and research support (*Editorial*), 1
- Glucagonomas, immunocytochemistry of, 607
- Glutamine in muscle affected by alanyl-glutamine, 637
- Growth hormone, and burn wound healing, 424

H

- Heart
  - artificial, electrically powered, 339
  - coronary artery reoperations, 378
  - myocardial effects of protamine, 387
  - replacement with skeletal muscle ventricles, 345
  - risks of abdominal aortic aneurysm repair in coronary artery disease, 415
  - rupture in blunt trauma, 701
  - suspected myocardial contusion, 82
  - transplantation of, and immunosuppression with FK 506, 295
- Heart failure from pneumonectomy in shock, 197
- Hypertension, intraoperative, preoperative predictors of, 66
- Hyperthermic perfusion, intraperitoneal, and surgery for gastric cancer, 592
- Hypotension, intraoperative, preoperative predictors of, 66
- Hypothermic circulatory arrest with cardiopulmonary bypass in retroperitoneal tumors, 472

I

- Ileal bypass, partial, in hypercholesterolemia, 318
- Ileoanal anastomosis results in polyposis and colitis (*Letters*), 120
  - and pouch-related complications, 446
- Ileoanal straight pull-through with total colectomy in benign colorectal disease, 242
- Ileus, postoperative, early ambulation affecting, 671
- Imipenem/cilastatin in intra-abdominal infections, 581
- Infections
  - enterococcal, recommendations for therapy in, 155
  - hepatic abscess management, 655
  - intra-abdominal
    - abscess after blunt trauma, 60
    - imipenem/cilastatin in, 581
  - morbidity with secondary cholecystectomy (*Letters*), 651
  - role of tumor necrosis factor in sepsis, 653
- Inhalation injury in burn trauma, 720
- Insulinomas
  - immunocytochemistry of, 607
  - occult, 615
- Interleukin-2
  - multisystem organ edema from, 728
  - receptor in trauma, 202
- Ischemia
  - hepatic, and effects of anesthetics, 23
  - lower-limb, aggressive salvage procedures in, 402
  - upper extremity, vascular access in, 187

J

- Jaundice, prevention of postoperative complications in, 221

K

Kidney transplantation
  and immunosuppression with FK 506, 295
  in infants, 353

L

Lactulose, and prevention of postoperative complications in jaundice, 221
Laser thermal angioplasty, 257
Letters to the editor, 118, 648
Leukocytes, dendritic, in allograft rejection, 308
Leukosequestration, systemic, from acid aspiration, tumor necrosis factor affecting, 513
Liver
  abscess management, 655
  Budd–Chiari syndrome management, 144
  estrogen receptors in hepatocellular carcinoma, 150
  ischemia of, and effects of anesthetics, 23
  nitric oxide production by hepatocytes, 462
  polycystic disease of, highly symptomatic, 30
  resection for disseminated testicular cancer, 290
  in sclerosing cholangitis, 551
  transplantation of
    and immunosuppression with FK 506, 295
    reduced-size grafts in, 368
    split-liver grafting in, 14
Lungs
  acid aspiration-induced injury affected by tumor necrosis factor, 513
  inhalation injury in burn trauma, 720
  microvascular injury after intestinal ischemia–reperfusion, and tumor necrosis factor activity, 694
  transplantation of, 249
    and immunosuppression with FK 506, 295
Lymph nodes, axillary dissection in melanoma, 125

M

Mallory–Weiss tears, and bleeding in urban hospital patients, 521
Melanoma
  axillary dissection in, 125
  current management of (*Editorial*), 123
  late recurrence of, 173
Metabolism
  intestinal, tumor necrosis factor affecting, 663
  protein, postoperative, oxygen supply affecting, 228
Metyrosine in pheochromocytoma, 621
Monitoring of patients, and postoperative outcome (*Editorial*), 559
Muscle
  protein synthesis affected by alanyl-glutamine, 637
  skeletal muscle ventricles for cardiac replacement, 345

N

Neutrophils in multisystem organ edema from interleukin-2, 728
Nitric oxide production by hepatocytes, 462

O

Obstruction
  gastric outlet, and parietal cell vagotomy and dilatation for peptic duodenal stricture, 597
  small bowel, postoperative (*Letters*), 121
  tracheobronchial, in infants and children, 277
Octreotide in postgastrectomy dumping syndrome, 678
Oxygen, and postoperative protein metabolism, 228

P

Pancreas
  cancer of
    and radical pancreatectomy in elderly patients, 140
    surgical palliation in, 132
  cystic tumors of, 432
  endocrine tumors of, 607
Pancreatectomy, radical, in elderly patients, 140
Pancreatitis, acute
  historical aspects of, 109
  and normoamylasemia (*Letters*), 648
Paraplegia, abdominal problems in, 561
Parathormone levels, and mortality in critically ill patients, 543
Parietal cell vagotomy and dilatation for peptic duodenal stricture, 597
Pelvic disease, intrarectal ultrasonagraphy in, 602
Pentobarbital affecting responses to liver ischemia, 23
Peptides in endocrine pancreatic tumors, 607
Pheochromocytoma, metyrosine in, 621
Platelet-activating factor in cholecystitis, 455
Pleural wrap for esophageal perforation (*Letters*), 652
Pneumatosis intestinalis, management of, 160
Pneumonectomy in shock, heart failure from, 197
Polyposis, familial adenomatous, ileoanal anastomosis in (*Letters*), 120
  pouch-related complications in, 446
Presidential address, 235
Prostaglandins
  intravenous infusion of PGE_1 inhibiting tumor growth, 45
  splanchnic PGI_2 production after reperfusion in shock, 688
Prostanoids, and cholecystitis produced by platelet-activating factor, 455
Protamine, myocardial effects of, 387
Protein
  muscle synthesis affected by alanyl-glutamine, 637
  postoperative metabolism affected by oxygen supply, 228
  synthesis by hepatocytes, inhibition of, 462

R

Research support in surgical programs (*Editorial*), 1
Retroperitoneal tumors
  cardiopulmonary bypass and deep hypothermic circulatory arrest in, 472
  sarcoma, 51

S

Schistosomiasis, and selective shunt versus nonshunt surgery in variceal bleeding, 97
Scoring systems, and evaluation of APACHE II for surgical patients, 266

Shock
  pneumonectomy in, heart failure from, 197
  and reperfusion affecting splanchnic PGI_2 production, 688
Spinal cord injury, abdominal problems in, 561
Stomach
  acute mucosal lesions in, and bleeding in urban hospital patients, 521
  colorectal cancer after partial gastrectomy, 714
  octreotide in postgastrectomy dumping syndrome, 678
  surgery and intraperitoneal hyperthermic perfusion for cancer, 592

T

Testicular cancer, disseminated, hepatic resection in, 290
Thrombi, vena caval, in tumors, cardiopulmonary bypass with deep hypothermic circulatory arrest in, 472
Thromboxane levels in multisystem organ edema from interleukin-2, 728
Thyroid carcinoma, medullary, hypercalcitoninemia in, 395
Tracheobronchial obstruction in infants and children, 277
Transplantations
  cardiac, and immunosuppression with FK 506, 295
  dendritic leukocytes in allograft rejection, 308
  of liver
    and immunosuppression with FK 506, 295
    reduced-size grafts in, 368
    split-liver grafting in, 14
  of lungs, 249
    and immunosuppression with FK 506, 295
  renal
    and immunosuppression with FK 506, 295
    in infants, 353
Trauma
  abdominal
    and CT scanning in comatose children (*Letters*), 118
    and intra-abdominal abscess, 60
  cardiac rupture after blunt trauma, 701
  of colon, primary repair of (*Letters*), 118
  interleukin-2 receptor in, 202
  suspected myocardial contusion, 82
Tumor
  axillary dissection in melanoma, 125
  breast conservation therapy for cancer
    in multiple tumors, 38
    and survival after locoregional recurrence, 166
  carcinoid, anorectal (*Letters*), 650
  colorectal cancer after partial gastrectomy, 714
  current management of melanoma (*Editorial*), 123
  cystic tumors of pancreas, 432
  endocrine pancreatic, 607
  estrogen receptors in hepatocellular carcinoma, 150
  growth inhibition by intravenous prostaglandin E_1, 45
  hepatic resection in disseminated testicular cancer, 290
  hypercalcitoninemia in medullary thyroid carcinoma, 395
  intraperitoneal hyperthermic perfusion and surgery for gastric cancer, 592
  intrarectal ultrasound in rectal cancer staging, 602
  metyrosine in pheochromocytoma, 621
  molecular physiology of cancer, 3
  occult insulinomas, 615
  palliation for pancreatic cancer, 132
  and pancreatectomy in elderly patients, 140
  soft-tissue sarcoma of retroperitoneum, 51
Tumor necrosis factor
  and acid aspiration-induced systemic organ injury, 513
  affecting intestinal structure and metabolism, 663
  and pulmonary microvascular injury after intestinal ischemia–reperfusion, 694
  role in sepsis, 653
Tyrosine hydroxylase inhibitor in pheochromocytoma, 621

U

Ulcer, peptic
  and bleeding in urban hospital patients, 521
  colorectal cancer after partial gastrectomy in, 714
  parietal cell vagotomy and dilatation for duodenal stricture in, 597
Ultrasonography, intrarectal, clinical uses of, 602
Urinary tract refunctionalization after long-term diversion, 478

V

Vagotomy, parietal cell, and dilatation for peptic duodenal stricture, 597
Variceal bleeding
  selective shunt versus nonshunt surgery in, 97
  in urban hospital patients, 521
Vasculature
  abdominal aortic aneurysm repair in coronary artery disease, 415
  angioaccess in upper extremity ischemia, 187
  carotid restenosis after endarterectomy, 629
  laser thermal angioplasty, 257
  late failure of reversed vein bypass grafts (*Letters*), 122
  pulmonary microvascular injury after intestinal ischemia–reperfusion, and tumor necrosis factor activity, 694
  salvage efforts in lower-limb–threatening ischemia, 402
  vascular complications of aortic dissection, 705
  verapamil affecting vein bypass graft patency, 87
Vein bypass grafts
  late failure of (*Letters*), 122
  patency affected by verapamil, 87
Vena cava thrombi in tumors, cardiopulmonary bypass in, with deep hypothermic circulatory arrest, 472
Verapamil affecting vein bypass graft patency, 87

W

Wound healing in burns, growth hormone affecting, 424

Author Index (July–December 1990)

A

Abu-Elmagd, K. M. 97
Abumrad, N. N. 678
Adami, H.-O. 714
Adzick, N. S. 277
Ales, K. L. 66, 567
Alessiani, M. 295
Alexander, J. W. 496
Alonso, E. A. 14
Alton, J. D. M. 720
Aly, M. A. 97
Amalric, R. 38
Anderson, C. B. 187
Anderson, D. R. 345
Andrus, C. H. 455
Angermeier, K. 472
Arbeit, J. M. 3
Ash, S. K. 496
Atkinson, J. B. 194
Atkinson, N. 166
Attwood, S. E. A. 528
Austyn, J. M. 308
Ayme, Y. 38

B

Babcock, G. F. 496
Bakal, C. W. 402
Baker, A. L. 368
Balch, C. M. 166
Barie, P. S. 155
Barrow, R. E. 424
Beart, R. W., Jr. 446
Bernstein, E. F. 629
Bevilacqua, R. G. 125
Biber, B. 23
Bies, L. E. 387
Billiar, T. R. 462
Bland, K. I. 45
Bolling, S. F. 387
Böttcher, G. 607
Boyce, S. T. 496
Braasch, J. W. 551
Braithwaite, C. E. M. 701
Brandone, H. 38
Branum, G. D. 655
Branum, M. A. 655
Brennan, L. P. 194
Brennan, M. F. 51, 125
Bressac, C. 38
Bridges, C. R., Jr. 345
Broelsch, C. E. 14, 368
Broemeling, L. 424
Brown, J. M. 178
Buchwald, H. 318
Bull, D. A. 561
Burchard, K. W. 543
Busse-Henry, S. M. 14
Busuttil, R. 581
Buurman, W. A. 221

C

Cameron, J. L. 144
Campos, C. T. 318
Cardenosa, G. 432
Caty, M. G. 694
Chaing, F. L. 257
Chang, Y.-C. 150
Charlson, M. E. 66, 567
Chavers, B. 353
Cherqui, D. 14
Chikenji, T. 592
Childress, C. P. 496
Christou, N. V. 155, 581
Chwals, W. J. 194
Civetta, J. M. 266
Coit, D. G. 51, 125
Coleman, J. 144
Coller, J. A. 209
Colliton, J. 543
Compton, C. C. 432
Cook, M. 353
Cooper, J. D. 249
Copeland, E. M., III 45
Coran, A. G. 242
Cosgrove, D. M. 378, 472
Cowley, RA. 701
Cromack, D. T. 615
Cross, K. S. 87
Crowley, N. J. 173
Cryer, H. G. 197
Cué, J. I. 197
Curran, R. D. 462
Cynamon, J. 402

D

Davidoff, A. M. 160
Dellinger, E. P. 155, 581
deLorimier, A. A. 277
DeMeester, T. R. 528
Demetris, A. J. 295
Desai, D. 213
Deshpande, Y. G. 455
Devine, R. M. 446
Dietzek, A. M. 402
Dilley, R. B. 629
Donachy, J. H. 339
Donaldson, M. C. 415
Donohue, J. P. 290
Doppman, J. L. 615
Dozois, R. R. 446
Dunham, C. M. 701
Dunn, D. L. 496

E

Einhorn, L. H. 290
El-Barbary, M. H. 97
El-Fiky, A. M. 97
El-Ghawlby, N. A. 97
Ellis, L. M. 45
El-Sanadiki, M. N. 87
Emond, J. C. 14, 368
Ezzat, F. A. 97

F

Fairston, B. A. 166
Fann, J. I. 705
Fathy, O. M. 97
Flint, S. G. 462
Foley, E. 551
Forster, J. 543
Foster, C. E., III. 194
Fraker, D. L. 615
Frey, D. J. 353
Fromm, D. 521
Fujimoto, S. 592
Fung, J. J. 295
Furuya, K. 228

G

Gagner, M. 551
Galandiuk, S. 446
Gann, D. S. 543
Geer, R. J. 678
German, D. 455
Gharib, H. 395
Gianotti, L. 496
Gillingham, K. J. 353
Girotti, M. J. 202
Gliedman, M. L. 402
Goins, W. A. 60
Gold, J. P. 66, 567
Golden, M. A. 415
Golding, L. A. R. 378
Goldman, G. 513, 728
Goldsmith, J. 402
Goormastic, M. 378, 472
Gorden, P. 615
Gorelick, F. S. 109
Goulet, R. J., Jr. 290
Gouma, D. J. 221
Graffner, H. 602
Grant, C. S. 395
Greve, J. W. 221
Grosfeld, J. L. 290
Guice, K. S. 694
Gupta, S. K. 402

H

Hagen, P.-O. 87
Hajdu, S. I. 51
Hammarqvist, F. 637
Hammond, R. L. 345
Hans, D. 38
Harbrecht, B. G. 462
Hardacre, J. M. 290
Hardy, K. 277
Harken, A. H. 178
Harrison, M. R. 277

Hasselgren, P.-O. 23
Hay, I. D. 395
Hayashi, T. 150
Hechtman, H. B. 513, 728
Helmick, C. 714
Hendren, W. H. 478
Herlong, F. H. 144
Herndon, D. N. 424
Hinder, R. A. 528
Hohenhaus, E. 345
Howell, L. J. 277
Hudson-Civetta, J. A. 266

I

Ilstrup, D. M. 395, 446

J

Jacobs, D. 60
Jacquemier, J. 38
Jacques, D. P. 51
Jain, A. 295
Jendrisak, M. D. 187
Jenkins, R. L. 551
Jensen, R. T. 615
Jones, J. A. 290
Joshi, M. 60

K

Kaminski, D. L. 455
Kaye, M. C. 472
Keiser, H. R. 621
Kelly, K. A. 446
Kim, S. W. 332
Kirsch, M. M. 387
Kitsukawa, Y. 592
Kiuchi, S. 592
Klein, A. S. 144
Klein, E. 472
Knechtle, S. J. 160
Kobayashi, K. 592
Kobzik, L. 513, 728
Kohno, H. 150
Kokubun, M. 592
Konno, C. 592
Kormos, R. 295
Kunkel, K. R. 424
Kunkel, S. I. 694
Kurtz, J. M. 38

L

Lalani, S. 202
Lally, K. P. 194
Larsen, C. P. 308
Leach, S. D. 109
Lewandrowski, K. 432
Lewis, W. D. 551
Lichtor, J. L. 368
Linehan, W. M. 621
Loehrer, P. J. 290
Longmire, W. P., Jr. 132
Loop, F. D. 378
Lundegärdh, G. 714
Lytle, B. W. 378

M

MacKenzie, C. R. 66, 567
Madura, J. A. 290
Maessen, J. G. 221
Mannick, J. A. 235, 415
March, R. J. 213
Mårtensson, H. 607
Martin, F. M. 551
Matas, A. J. 353
Matts, J. P. 318
Mauer, S. M. 353
Mavroudis, C. 197
McCann, R. L. 87
McNeese, M. 166
McRitchie, D. I. 202
Mealy, K. 663
Mehringer, M. C. 257
Menteş, A. Ş. 597
Meyers, W. C. 655
Michie, H. R. 653
Mikat, E. 87
Miller, D. C. 705
Miller, D. L. 615
Milsom, J. W. 602
Mimura, Y. 228
Mitchell, R. S. 705
Mizutani, M. 592
Modlin, I. M. 109
Mohr, J. D. 561
Montie, J. E. 472
Morris, P. J. 308
Morton, D. L. 123
Moysa, G. L. 720
Mueller, P. R. 432
Murray, J. J. 87, 209
Myers, S. I. 688

N

Nagasue, N. 150
Nagorney, D. M. 30, 140
Najarian, J. S. 353
Nakamura, R. 521
Nakamura, T. 150
Nelson, L. D. 266
Neumayer, L. A. 561
Nevins, T. E. 353
Newman, K. D. 30
Niederhuber, J. E. 1
Niinami, H. 345
Nivatvongs, S. 446
Nobin, A. 607
Nordström, G. 23
Norton, J. A. 615, 621
Novick, A. C. 472
Nugent, F. W. 551

O

Ochoa, J. B. 462
O'Dorisio, T. M. 678
Ohta, M. 592
Okui, K. 592
Oldham, K. T. 694
Oohara, T. 228
Oswald, M. J. 166
Oyer, P. E. 705

P

Pae, W. E., Jr. 339
Parekh, D. 332
Pass, H. I. 621
Peck, M. D. 496
Pemberton, J. H. 446
Perry, R. R. 621
Peters, W. J. 202
Pierce, W. S. 339
Pochettino, A. 345
Polk, H. C., Jr. 197
Pontes, J. E. 472
Putnam, C. W. 561
Pyles, T. 496

R

Rakela, J. 30
Reber, H. A. 132
Redmond, M. L. 213
Reed, W. H. 82
Remick, D. G. 694
Reves, J. G. 559
Rice, D. 678
Rice, R. P. 160
Richards, W. O. 678
Richardson, J. D. 197
Riddick, R. S. 82
Rivers, S. P. 402
Roberts, A. M. 197
Roberts, P. L. 209
Robertson, C. N. 621
Rodgriguez, A. 701
Rodriguez, A. 60
Rogatko, A. 125
Rosenberg, G. 339
Rossi, R. L. 551
Rout, W. R. 155
Rutan, R. L. 424

S

Salmons, S. 345
Samet, P. 345
Sarr, M. G. 140
Sarris, G. E. 705
Schirmer, B. D. 671
Schoetz, D. J. 209
Scholz, F. J. 551
Schuman, R. W. 87
Scott, N. A. 446
Seigler, H. F. 173
Sferra, C. S. 521
Sferra, J. J. 521
Shankowsky, H. A. 720
Shapiro, R. 295
Sharefkin, J. B. 178

Shawker, T. H. 615
Shepro, D. 513, 728
Shires, G. T. 66, 567
Shrestha, R. D. 592
Shumway, N. E. 705
Simmons, R. L. 462
Singh, S. M. 132
Sitren, H. S. 45
Sitzmann, J. V. 144
Smith, L. R. 559
Smyrk, T. C. 528
Snyder, A. J. 339
So, S. S. K. 353
Solomkin, J. S. 581
Spanta, A. D. 345
Spencer, M. P. 140
Spitalier, J.-M. 38
Sprayregen, S. 402
Stanislawska, M. 688
Stanley, J. C. 387
Starzl, T. E. 295
Steffes, C. P. 521
Stephenson, L. W. 345
Stewart, R. 472
Stewart, R. W. 378
Stinson, E. B. 705
Stoller, D. K. 318
Stone, H. H. 155
Stotter, A. 166
Streem, S. B. 472
Stuehr, D. J. 462
Sugawa, C. 521
Sugimura, Y. 521
Sundler, F. 607

T

Taerum, T. V. 720
Takahashi, M. 592
Takaya, S. 295
Taylor, B. J. 688
Taylor, P. C. 378
Teodorczyk-Injeyan, J. A. 202
Therkildsen, D. H. 528
Thislethwaite, J. R. 14
Thistlethwaite, J. R. 368
Thompson, J. C. 332
Tiebosch, T. 221
Todo, S. 295
Topkins, M. 66, 567
Torem, S. 629
Torres, V. E. 30
Townsend, C. M., Jr. 332
Travis, W. 621
Tredget, E. E. 720
Turney, S. Z. 701
Tyson, G. S. 655
Tzakis, A. 295

V

Valeri, C. R. 513, 728
van Heerden, J. A. 395
van Lanschot, J. J. B. 663
Varco, R. L. 318
Veidenheimer, M. C. 209
Veith, F. J. 402
Vinnars, E. 637
Vogelbach, P. 14
von der Decken, A. 637

W

Wakefield, T. W. 387
Waldhausen, J. A. 339
Waldhausen, J. H. T. 671
Wall, R. T. 621
Walther, M. M. 621
Warshaw, A. L. 432
Watters, J. M. 213
Waymack, J. P. 155
Welbourn, R. 513, 728
Wengerter, K. R. 402
Wernerman, J. 637
White, G. H. 257
White, R. A. 257
Whitington, P. F. 14, 368
Whittemore, A. D. 415
Williams, S. 678
Wilmore, D. W. 653, 663
Wilson, S. E. 257
Winsö, O. 23
Wisner, D. H. 82
Wolff, B. G. 446
Woltering, E. O. 678
Woodle, I. S. 14
Woods, E. L. 378
Wrobleski, S. K. 387

Y

Yamakawa, M. 228
Yamanoi, A. 150
Younes, R. N. 125
Yu, J. 197
Yukaya, H. 150

Z

Zack, M. 714
Zucker, A. R. 14

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Index to Advertisers

Appleton & Lang .... Cover 3
Academic 12A
Candela Laser Corp............... 11A, 13A
Classified Advertising 22A-24A
Cook County Graduate School 21A
Garrett County Hospital 25A
Lahey Clinic Medical Center 21A
J.B. Lippincott Co. 16A, 18A, 26A
Kaiser Permanente (Norther California) .. 25A
Medical College of Pennsylvania 21A
Merck, Sharp & Dohme 8A-10A
Moss Tubes 14A
Norwich Eaton 4A
Parke Davis .... Cover 4
Regent Hospital 2A
Squibb & Son 19A-20A
Stuart Pharmaceuticals ....Cover 2 -1A
University of Chicago 25A
WSB Space 17A

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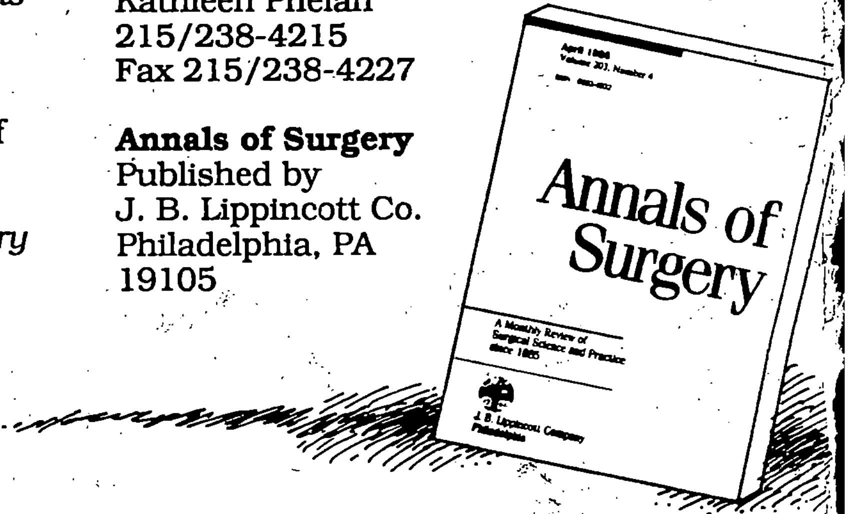
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